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Review

Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: A critical review of recent literature ☆, ☆☆

Gloria B. Post [a,*], Perry D. Cohn [b], Keith R. Cooper [c]

[a] Office of Science, New Jersey Department of Environmental Protection, Mail Code 428-01, P.O. Box 420, Trenton, NJ 08625, USA
[b] Consumer, Environmental, and Occupational Health Service, New Jersey Department of Health and Senior Services, P.O. Box 369, Trenton, NJ 08625, USA
[c] Department of Biochemistry and Microbiology, Rutgers University, 76 Lipman Drive, New Brunswick, NJ 08901, USA

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ABSTRACT

Perfluorooctanoic acid (PFOA) is an anthropogenic contaminant that differs in several ways from most other well-studied organic chemicals found in drinking water. PFOA is extremely resistant to environmental degradation processes and thus persists indefinitely. Unlike most other persistent and bioaccumulative organic pollutants, PFOA is water-soluble, does not bind well to soil or sediments, and bioaccumulates in serum rather than in fat. It has been detected in finished drinking water and drinking water sources impacted by releases from industrial facilities and waste water treatment plants, as well as in waters with no known point sources. However, the overall occurrence and population exposure from drinking water is not known. PFOA persists in humans with a half-life of several years and is found in the serum of almost all U.S. residents and in populations worldwide. Exposure sources include food, food packaging, consumer products, house dust, and drinking water. Continued exposure to even relatively low concentrations in drinking water can substantially increase total human exposure, with a serum:drinking water ratio of about 100:1. For example, ongoing exposures to drinking water concentrations of 10 ng/L, 40 ng/L, 100 ng/L, or 400 ng/L are expected to increase mean serum levels by about 25%, 100%, 250%, and 1000%, respectively, from the general population background serum level of about 4 ng/mL. Infants are potentially a sensitive sub-population for PFOA's developmental effects, and their exposure through breast milk from mothers who use contaminated drinking water and/or from formula prepared with contaminated drinking water is higher than in adults exposed to the same drinking water concentration. Numerous health endpoints are associated with human PFOA exposure in the general population, communities with contaminated drinking water, and workers. As is the case for most such epidemiology studies, causality for these effects is not proven. Unlike most other well-studied drinking water contaminants, the human dose-response curve for several effects appears to be steepest at the lower exposure levels, including the general population range, with no apparent threshold for some endpoints. There is concordance in animals and humans for some effects, while humans and animals appear to react differently for other effects such as lipid metabolism. PFOA was classified as "likely to be carcinogenic in humans" by the USEPA Science Advisory Board. In animal studies, developmental effects have been identified as more sensitive endpoints for toxicity than carcinogenicity or the long-established hepatic effects. Notably, exposure to an environmentally relevant drinking water concentration caused adverse effects on mammary gland development in mice. This paper reviews current information relevant to the assessment of PFOA as an emerging drinking water contaminant. This information suggests that continued human exposure to even relatively low concentrations of PFOA in drinking water results in elevated body burdens that may increase the risk of health effects.

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; C8, synonym for perfluorooctanoic acid (PFOA); BMD, benchmark dose; BMDL, benchmark dose lower confidence interval; diPAPs, polyfluoroalkyl phosphoric acid diesters; ECF, electrochemical fluorination; FTOH, fluorotelomer alcohol; GD, gestation day; GGT, gamma-glutamyl transpeptidase; KO, knockout: LDH, serum lactic acid dehydrogenase; LOAEL, lowest observed adverse effect level; MOA, mode of action; NHANES, National Health and Nutrition Examination Survey; NOAEL, no observed adverse effect level; OATs, organic anion transporters; PFC, perfluorinated chemical; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PND, postnatal day; PPAR, peroxisome proliferator-activated receptor; PTFE, polytetrafluoroethylene; T3, triiodothyronine; T4, thyroxine; USEPA, United States Environmental Protection Agency; WT, wild type; WY, Wyeth 14,643.

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* Corresponding author: Fax: +1 609 292 7340.
E-mail addresses: gloria.post@dep.state.nj.us (G.B. Post), perry.cohn@doh.state.nj.us (P.D. Cohn), cooper@aesop.rutgers.edu (K.R. Cooper).

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Contents

1. Introduction

Perfluorooctanoic acid (PFOA; C8) is a member of the class of substances called perfluorinated chemicals (PFCs). The chemical formula of PFOA is $CF_3(CF_2)_6COOH$. PFOA and other PFCs do not occur naturally, and they have been produced and used in commercial products and industrial processes for over 60 years (Lindstrom et al., 2011a). Their useful properties, including oil- and water-repellency and resistance to heat and chemical reactions, are due to their structure, which includes a totally fluorinated carbon chain that is both hydrophobic and oleophobic and a hydrophilic charged functional group such as carboxylic or sulfonic acid. They are used in water-, soil-, and stain-resistant coatings for clothing, leather, upholstery, and carpets; oil-resistant coatings for food contact paper; aviation hydraulic fluids; fire-fighting foams; paints, adhesives, waxes, polishes, and other products; and industrially as surfactants, emulsifiers, wetting agents, additives, and coatings. PFOA is used as a processing aid (emulsifier) in the production of polytetrafluoroethylene (PTFE) and other fluoropolymers and fluoroelastomers which are used as non-stick coatings on cookware, membranes for waterproof/breathable clothing, electrical wire casing, fire and chemical resistant tubing, and plumbing thread seal tape (Lau et al., 2007; ATSDR, 2009).

PFOA and other PFCs have been made by two major manufacturing methods, electrochemical fluorination (ECF) and telomerization (Buck et al., 2011; Lindstrom et al., 2011a). ECF produces a mixture of compounds including branched, linear, and cyclic isomers of various chain lengths, while telomerization produces primarily straight chain (linear) compounds with an even number of carbons, such as PFOA. Isomer profiling methods may be used to assess the relative contribution from each of these manufacturing processes to PFOA found in environmental and biological media (De Silva and Mabury, 2006; De Silva et al., 2009a; Benskin et al., 2010).

Currently, attention is focused on PFOA and other PFCs as emerging environmental contaminants, and a large body of new information is available about their environmental occurrence, fate, and transport, as well as human exposure, pharmacokinetics, epidemiology, toxicology, and mode of action. PFCs are extremely persistent and are very resistant to typical environmental degradation processes due to their carbon–fluorine bonds, one of the strongest found in organic chemistry (Vaalgamaa et al., 2011). They are found in environmental media worldwide, including finished drinking water, surface water, groundwater, air, sludge, soils, sediments, outdoor and indoor dust, biota, and polar ice caps (Lau et al., 2007; ATSDR, 2009).

The manufacture and use of PFOA is currently being phased out by eight major manufacturers through a voluntary stewardship agreement with USEPA to reduce global facility emissions and product content of PFOA and related chemicals by 95% by 2010, and to work toward eliminating emissions and product content by 2015 (USEPA, 2010a,2012). However, environmental contamination and human exposure from PFOA are anticipated to continue for the foreseeable future due to its persistence, formation from precursor compounds (Section 2.2), and the potential for continued production by other manufacturers in the U.S. and/or overseas (USEPA, 2009a; Lindstrom et al., 2011a).

Lindstrom et al. (2011a) provide a recent general overview of current issues related to PFCs in the environment; other comprehensive general reviews include Lau et al. (2007), EFSA (2008), and ATSDR (2009). Recent reviews of information about PFOA, many of which also cover other PFCs, have focused on endocrine disrupting properties (White et al., 2011a); effects on the immune system (Dewitt et al., 2012); dietary exposures (D'Hollander et al., 2010; Domingo, 2012); production processes and formation from precursor compounds (Buck et al., 2011); importance in the aquatic environment (Ahrens, 2011) including drinking water sources (Murray et al., 2010); and on PFCs in biosolids applied to agricultural land (Clarke and Smith, 2011), municipal landfill leachates (Eggen et al., 2010), hazardous waste sites (Ela et al., 2011), and biota (Houde et al., 2011). PFCs, including PFOA, were one of the first four groups of existing chemicals for which the USEPA Office of Pollution Prevention and Toxics recently

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developed Action Plans, an initial step in addressing their risks (USEPA, 2009a).

PFOA is found in groundwater and surface water contaminated by discharges from industrial facilities, as well as in waters not known to be impacted by a point source (Mak et al., 2009; Post et al., 2009a). Health-based drinking water guidelines for PFOA previously developed by several government agencies around the world are reviewed by Zushi et al. (2012). However, many of the recent studies in human and experimental animals, some of which show effects at low doses (Section 6), were not considered in the development of these guidelines. Two PFCs, PFOA and perfluorooctane sulfonate (PFOS), are included in the USEPA Contaminant Candidate List 3 of chemicals under consideration for future drinking water regulation in the U.S. (USEPA, 2009b). The USEPA Science Advisory Board (USEPA, 2009c) recommended that PFOA be given a high priority for drinking water regulation based on its occurrence, health effects, and availability of treatment removal technology. Additionally, PFOA and five other PFCs are listed in the proposed Unregulated Contaminant Monitoring Rule 3 (USEPA, 2011) which, if finalized as proposed, will require nationwide monitoring by public water supplies to provide occurrence data needed for regulatory decision making.

PFOA's properties differ from those of other persistent and bioaccumulative organic pollutants such as polychlorinated dioxins and furans, PCBs, and pesticides like chlordane and DDT. These compounds are generally not significant as drinking water contaminants because they have high octanol/water partition coefficients, and thus high affinity for sediments and low water solubility. The primary source of human exposure to these lipid-soluble compounds is dietary, from lipids in fish, meat, and dairy products, and they have long half-lives in humans, where they are stored in fat (Post et al., 2011).

In contrast, PFOA, as well as some other PFCs, are distinctive as persistent and bioaccumulative organic compounds that are known to be important drinking water contaminants. PFOA exists predominantly as an anion under environmental conditions, migrates readily from soil to groundwater, and is highly water-soluble (Davis et al., 2007). As discussed in Section 4.2.1, drinking water can be an important source of human exposure. Like the other compounds discussed above, it is persistent in humans, with a half-life of several years, but it accumulates primarily in the serum, liver, and kidney, rather than in the fat (Lau et al., 2007).

PFOA's unique characteristics, including its chemical properties, environmental fate, toxicokinetics, and health effects, distinguish it from other commonly detected and currently regulated drinking water contaminants. Recent animal toxicology and human epidemiology studies suggest that continued exposure to even relatively low concentrations of PFOA in drinking water result in elevated body burdens that may increase the risk of health effects. This paper reviews current information relevant to the assessment of PFOA as an emerging drinking water contaminant.

2. Fate and transport relevant to drinking water contamination

2.1. Sources of water contamination

Environmental transport pathways relevant to surface water and groundwater contamination by PFOA released from a point source (Fig. 1, Davis et al., 2007) were reviewed by Lau et al. (2007) and Butt et al. (2010).

Like other groundwater contaminants, PFOA can reach drinking water wells via the well-established pathway of migration of a contaminated groundwater plume. PFOA, unlike many other environmental contaminants, can also reach groundwater from air emissions from nearby industrial facilities, followed by deposition from air onto soil and migration through the soil to groundwater (Davis et al., 2007).

In West Virginia and Ohio, drinking water wells as far as 20 miles away were contaminated by releases from an industrial facility. This occurred via soil deposition of PFOA that had been emitted into the air, followed by migration to groundwater and, to some extent, recharge of the groundwater aquifer with contaminated surface water from the Ohio River (Steenland et al., 2009a; Shin et al., 2011). It was detected in public water supply wells in this vicinity at levels up to >4000 ng/L (DuPont and URS Diamond Corporate Remediation Group, 2008) and in private wells up to over 13,000 ng/L (Hoffman et al., 2011). In New Jersey, PFOA was detected at up to 190 ng/L in shallow unconfined wells of a public water supply located near an industrial source (Post et al., 2009a), and at >40 ng/L, with a maximum above 400 ng/L, in 59 of 104 private wells within a radius of slightly more than 2 miles of this facility (DuPont, 2009); contamination of the distant wells was likely due to air deposition.

PFOA can also enter groundwater or surface water used for drinking water from sources other than industrial releases. These include discharge from wastewater treatment plants treating domestic and/or industrial waste (Sinclair and Kannan, 2006), street runoff (Murakami et al., 2009), storm water runoff (Kim and Kannan, 2007), release of aqueous firefighting foams (Moody et al., 2003; Weiß et al., 2012), land application of biosolids (sludge) (Clarke and Smith, 2011; Lindstrom et al., 2011b; Sepulvado et al., 2011), land application of wastewater from industrial sources (Konwick et al., 2008), and use of contaminated industrial waste as a soil amendment (Skutlarek et al., 2006; Hölzer et al., 2008).

2.2. Formation of PFOA from precursor compounds

An additional source of PFCs in the environment is the breakdown of precursor compounds such as fluorotelomer alcohols (FTOH), used industrially and in consumer products (Butt et al., 2010; Buck et al., 2011). For example, 8:2 FTOH [$CF_3(CF_2)_7CH_2CH_2OH$] is converted to PFOA to some extent. Larger molecules, polyfluoroalkyl phosphoric acid diesters (diPAPs), such as diPAPs 8:2 (Fig. 2), found in greaseproof food contact papers, wastewater treatment plant sludge, and paper fibers from paper mills (D'eon et al., 2009), release FTOH that can degrade to PFOA. PFOA is formed from these precursor compounds through biodegradation in soil, sludge, and wastewater (Sinclair and Kannan, 2006; Lee et al., 2010), as well as through chemical reactions in the atmosphere. Fluoroacrylate polymers, used in commercial products, may also degrade in soil to release FTOH which can degrade to PFCs such as PFOA (Russell et al., 2008; Washington et al., 2009). Since PFOA does not degrade appreciably, environmental PFOA levels are increased by conversion of even a small fraction of the precursors to the terminal breakdown product, PFOA.

2.3. Long range transport pathways

Two major pathways have been proposed for long-range transport of PFCs, including PFOA, to remote locations worldwide, including the Arctic where they are found in aqueous media and wildlife (Lau et al., 2007; Butt et al., 2010); the relative contributions of each of these pathways are not known. The first pathway involves the atmospheric transport of volatile precursors, such as FTOH, followed by oxidation to PFOA and other PFCs which are then deposited onto the land or the water. The second pathway involves long-range aqueous transport of emitted perfluorinated carboxylates such as PFOA in their anionic forms to remote locations by currents on the ocean's surface.

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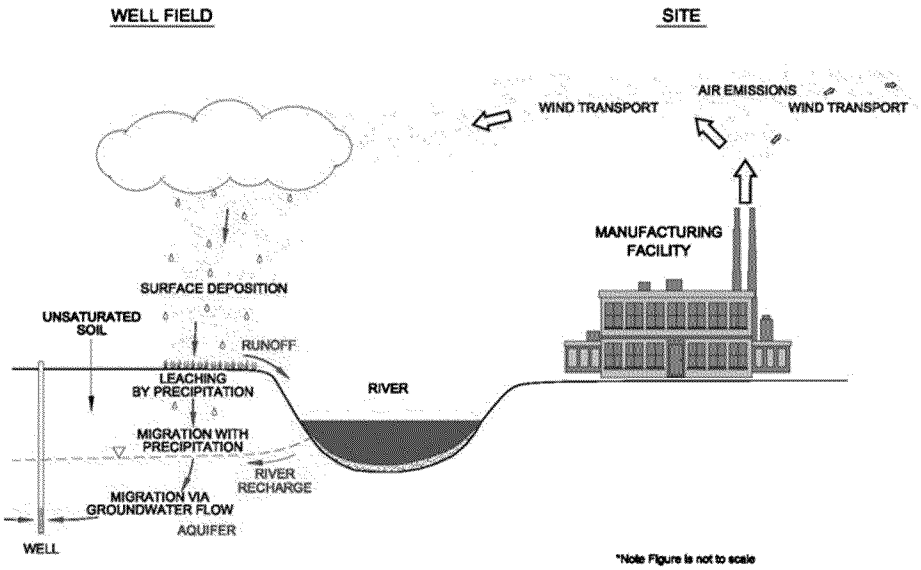

Fig. 1. Ammonium perfluorooctanoate (PFOA) transport near discharge source (Davis et al., 2007).

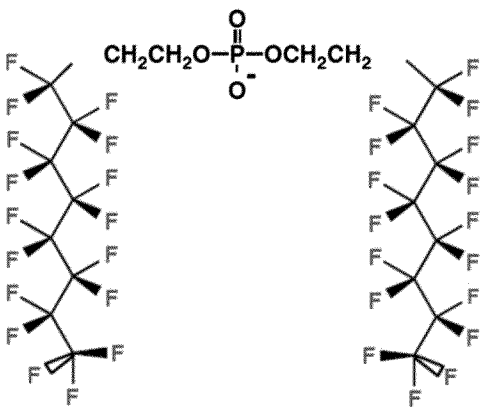

Fig. 2. Structure of diPAPs 8:2.

3. Occurrence in drinking water and source waters

PFOA and other PFCs occur in ground and surface sources of drinking water, and in raw and finished public drinking water in the United States and around the world (reviewed by ATSDR, 2009; Mak et al., 2009; Rumsby et al., 2009). Most of these studies focused on limited regions or on sites known or suspected to be contaminated. Because national drinking water occurrence surveys have not been conducted in the U.S. or other nations, conclusions cannot currently be made about the overall frequency and levels of occurrence in public water supplies or private wells, or about the number of people exposed above various concentration thresholds. In the U.S., the proposed Unregulated Contaminant Monitoring Rule 3 (USEPA, 2011), if finalized as proposed, will ultimately provide information on nationwide occurrence in public water supplies. PFOA is not removed from drinking water by standard treatment processes such as coagulation, sand filtration, sedimentation, ozonation, or chlorination, but can be removed by activated carbon (Rumsby et al., 2009; Bartell et al., 2010a; Takagi et al., 2011; Eschauzier et al., in press).

PFOA has been detected at high frequency in several river basins that are important sources of drinking water. For example, PFOA was detected at >1 ng/L in 82.3% of samples from 80 locations throughout the Cape Fear River (North Carolina) drainage basin, population 1.7 million, at a median of 12.6 ng/L and a maximum of 287 ng/L (Nakayama et al., 2007). In the Upper Mississippi River drainage basin in the Midwestern U.S., population 30 million, it was detected at >1 ng/L in 73% of 88 locations with a median of 2.07 ng/L and a maximum of 125 ng/L. Elevated levels at certain sites were attributed to point sources in this study (Nakayama et al., 2010). In the Tennessee River in Alabama, PFOA levels were 395 ± 128 ng/L in samples from the 35 river miles downstream of the site of discharge of effluent from a fluorochemical manufacturing facility, with the highest levels (521–598 ng/L) in the six river miles furthest downstream (Hansen et al., 2002). In Germany, PFOA and other PFCs in organic material applied to agricultural land contaminated the Moehne and Ruhr Rivers, important sources of drinking water. PFOA was detected at up to 33,900 ng/L in a creek near the site of contamination upstream of these rivers, and at up to 519 ng/L in drinking water from the Moehne River (Skutlarek et al., 2006).

Following detection of PFOA in two New Jersey public water supplies (PWS), two statewide studies of its occurrence in drinking water were conducted (Post et al., 2009a; NJDEP, 2011). The studies included both PWS intended to represent New Jersey geographically and other PWS selected for their potential vulnerability to PFC and/or synthetic organic chemical contamination. PFOA was quantified above the reporting limits of 4–5 ng/L in 59% of the 56 PWS tested, including those with groundwater and surface water sources, at levels up to >100 ng/L. To our knowledge, no other statewide occurrence studies of PFOA in public drinking water supplies have been conducted. In a similar study in Catalonia, Spain, PFOA was detected at >0.85 ng/L in 65% of 40 municipal water systems at mean, median, and maximum of 4.57 ng/L, 0.98 ng/L, and 57.43 ng/L, respectively (Ericson et al., 2009).

In a study of six U.S. public water systems impacted to varying degrees by treated wastewater, PFOA levels ranged from non-detect (<5 ng/L) to 120 ng/L, generally increasing with greater impact from treated wastewater (Quiñones and Snyder, 2009).

4. Human exposure and serum levels

4.1. Serum levels

Because PFOA persists in the serum of humans with a half-life of several years, human serum levels are a reliable and stable

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measure of internal dose. PFOA and other PFCs are present in the serum of the general population in the United States and worldwide (Kannan et al., 2004; reviewed by Lau et al., 2007; EFSA, 2008; Vestergren and Cousins, 2009). Serum levels reported from industrialized countries around the world are reasonably consistent, with arithmetic means of 2–8 ng/mL for most studies (Vestergren and Cousins, 2009). In making general comparisons about relative serum levels in different regions of the world, it must be recognized that the studies differ in design, time when conducted, analytical method, approaches and assumptions used in data analysis, and other factors.

The largest studies of the U.S. general population are the National Health and Nutrition Examination Survey (NHANES; Calafat et al., 2007; Kato et al., 2009; Kato et al., 2011) and studies of American Red Cross blood donors (Olsen et al., 2008). In the 2007–2008 NHANES, PFOA was found at >0.1 ng/mL in the serum of 99.9% of 2100 participants aged 12 or older, selected to provide a cross-sectional representation of the U.S. population (Kato et al., 2011). The geometric mean, 75th, 90th, and 95th percentile values were 4.13 ng/mL, 5.9 ng/mL, 7.9 ng/mL, and 9.7 ng/mL, respectively. Concentrations were similar in all age groups, and were higher in males (geometric mean, 4.80 ng/mL) than females (geometric mean, 3.56 ng/mL). Mexican-Americans had lower concentrations than non-Hispanic whites or non-Hispanic blacks. In the last three NHANES (2003–2004, 2005–2006, and 2007–2008), geometric mean serum levels have remained stable at about 4 ng/mL, slightly lower than the 1999–2000 value of 5.2 ng/mL (Kato et al., 2011).

PFOA serum levels were slightly lower than the 2007–2008 U.S. NHANES geometric mean of 4.13 ng/mL (Kato et al., 2011) in three smaller 2008–2009 European studies of about 200 adults each. Arithmetic means were about 2 ng/mL in Greece (Vassiliadou et al., 2010) and 3.6 ng/mL in Flanders, Belgium (Cornelis et al., 2012), and the geometric mean was 3.32 ng/mL in Italy (Ingelido et al., 2010). The mean was higher, 6.4 ng/mL, in 84 pooled serum samples from 2420 individuals (all ages) collected in 2006–2007 in Queensland, Australia (Toms et al., 2009). In contrast to industrialized nations where serum PFOA is almost universally detected, PFOA was detected at >0.5 ng/mL in only 12 of 55 serum samples from Afghan children and adults with a maximum of 1.5 ng/mL; relatively low serum levels have also been reported in other developing countries where exposure to PFOA and other PFCs may be lower than in industrialized nations (Hemat et al., 2010).

PFOA in pooled serum samples from children (age 3–11) in 2001–2002 NHANES ranged from about 6–8 ng/mL, significantly higher than in pooled serum samples from adults in this study (Kato et al., 2009). Median and maximum PFOA serum levels in 300 Texas children, age <1 to 12 years, were 2.85 ng/mL and 13.50 ng/mL; adults were not included in this study. In the Texas study, the median level did not differ between genders, and was lower in those <3 years of age than in the older age groups (Schecter et al., in press).

Data from archived serum samples from the United States and Norway indicate that human exposure to PFOA has been ongoing for decades, and that exposure increased greatly in the 1980s in these two locations. Analysis of serum samples collected up to 50 years ago found that the median level in serum from pregnant California women sampled in 1960–1963 ($n=40$) was 0.27 ng/mL, approximately 10-fold lower than median in serum from California women sampled in 1981–1986 ($n=30$) and 2009 ($n=35$), which were 2.71 and 2.08 ng/mL, respectively (Wang et al., 2011a). In pooled serum samples from Norwegian men (age 40–50) collected over a 29-year period (1977–2006), PFOA levels gradually increased from 0.58 ng/mL in 1977 to 4.9 ng/mL in 2001, an 8-fold increase, followed by a yearly decline to 2.7 ng/mL in 2006. A similar temporal pattern was seen in serum samples collected from Norwegian children and from male and female adults of various age groups between 1976 and 2007 (Haug et al., 2009).

Serum levels in workers making or using PFOA are much higher than in the general population (Lau et al., 2007; EFSA, 2008). Maximum concentrations in the 1990s in these workers were above 100,000 ng/mL (100 ppm), although the levels in most workers were far lower (ATSDR, 2009; EFSA, 2008). Serum levels in populations exposed to PFOA from contaminated drinking water are discussed in Sections 4.2.1 and 5.1.

As discussed in detail in Section 5.2, PFOA is also detected in human umbilical cord blood and breast milk, demonstrating that exposures relevant to potential developmental effects occur during prenatal and postnatal development.

4.2. Exposure sources

The human body burden of PFOA results both from exposure to PFOA itself and to precursor compounds, such as FTOH and diPAPs, which can be metabolized to PFOA (D'eon and Mabury, 2011a; Lee and Mabury, 2011). The relative contributions from direct exposure to PFOA and from exposure to its precursors, which are used in products including food contact paper and stain resistant carpet and textile coatings, are not known (D'eon and Mabury, 2011b).

Sources of exposure to PFOA and/or its precursors include drinking water, food, migration from food packaging into food, treated fabrics (carpets, upholstery, and clothing), house dust, use of protective sprays sold as consumer products, ski waxes, and inhalation of indoor and outdoor air (Trudel et al., 2008; Guo et al., 2009; Gewurtz et al., 2009; Freberg et al., 2011; Nilsson et al., 2010; Fraser et al., 2011). Migration into food from non-stick (PTFE-coated) cookware is not considered to be a significant exposure source (Trudel et al., 2008). Occupational exposure is believed to occur primarily through inhalation (ATSDR, 2009; Vestergren and Cousins, 2009).

Efforts have been made to model the relative contributions of consumer products, indoor and outdoor air, house dust, diet, and/or other sources to exposures of PFOA and other PFCs in the general population. Some of these studies estimated the contributions of precursors (Fromme et al., 2009; Vestergren and Cousins, 2009) while others did not (Washburn et al., 2005; Tittlemier et al., 2007; Trudel et al., 2008; Cornelis et al., 2012); a high level of uncertainty is associated with these precursor estimates.

Most of these studies predict that diet is the predominant exposure source. Typical adult total exposures of about 2–3 ng/kg/day in Europe or North American were estimated in several studies (Fromme et al., 2009; Trudel et al., 2008; Vestergren and Cousins, 2009), while some more recent studies give higher dietary estimates (6.1 ng/kg/day in Flanders, Belgium; Cornelis et al., 2012) or lower dietary estimates (0.6 ng/kg/day in Norway (Haug et al., 2010a); 0.2 ng/kg/day in The Netherlands (Noorlander et al., 2011)). Such dietary exposure estimates, in general, are highly uncertain because there are relatively few data on PFOA levels in food, analytical methods for food lack sufficient sensitivity, detection limits vary greatly among food types, and PFOA levels differ greatly in samples of the same foods obtained from different sources and/or locations.

PFOA has been detected in at least some samples of several types of foods including milk, butter, meats, fish, vegetables (including potatoes), bread, microwave popcorn, but was not detected in most food samples tested (reviewed by D'Hollander et al., 2010; Domingo, 2012). PFOA and other PFCs can be taken up into plants grown on contaminated soil (e.g., from application of PFOA-contaminated sewage sludge), including into the parts of some vegetables and grains that are consumed by humans and by

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grazing livestock (Stahl et al., 2009; Lechner and Knapp, 2011; Yoo et al., 2011). PFOA is much less bioaccumulative in fish than other PFCs with a longer fluorinated carbon chain (Conder et al., 2008). Thus, consumption of fish from waterways contaminated with PFOA does not result in the high exposures typical of other persistent organic contaminants, including PFOS, which are bioaccumulative in fish (Hölzer et al., 2011). However, PFOA has been detected in edible fish and other seafood, and consumption of aquatic organisms may represent a significant portion of total dietary exposure in some populations (Haug et al., 2010b; Zhang et al., 2011).

Several recent studies suggest that exposure to PFOA and its precursors from indoor air and/or house dust may be a major exposure source for some individuals (Haug et al., 2011; Shoeib et al., 2011). Fraser et al. (2011) report that the concentration of the PFOA precursor, 8:2 FTOH, in indoor air in offices is a predictor of serum PFOA concentration. Levels of this compound were greatly elevated in offices with new carpets compared to other offices.

Greater exposures to PFOA may occur in young children than in older individuals because of age-specific behaviors such as greater drinking water and food consumption on a body weight basis, hand-to-mouth behavior resulting in greater ingestion of house dust, and more time spent on floors where treated carpets are found (Section 5.1; Trudel et al., 2008; Shoeib et al., 2011).

4.2.1. *Exposure from drinking water*

The exposure studies discussed above provide varying conclusions about the relative importance of drinking water to total exposure; these conclusions are highly dependent on the concentration of PFOA in drinking water assumed in the analyses. For example, Fromme et al. (2009) and Cornelis et al. (2012) conclude that drinking water contributes $<1\%$ to total exposure, assuming drinking water levels of 1 ng/L and 2 ng/L, respectively, while Noorlander et al. (2011) estimate that 55% of exposure comes from drinking water, assuming 9 ng/L. Vestergren and Cousins (2009) and Thompson et al. (2011) demonstrate that the contribution of drinking water to total exposure depends on the concentration of PFOA. Thompson et al. (2011) predict that a drinking water level of 9.66 ng/L contributes 24% to total exposure; this is consistent with our estimate (below) of a 20% contribution from a drinking water level of 10 ng/L.

It is well established that serum concentrations are elevated in communities with highly contaminated drinking water resulting from known environmental discharges of PFOA (Emmett et al., 2006; Hölzer et al., 2008; MDH, 2009; Steenland et al., 2009a; Hoffman et al., 2011). For example, the median serum concentration in about 70,000 individuals using contaminated drinking water (50 to >3000 ng/L) in Ohio and West Virginia was 28.2 ng/mL, compared to about 4 ng/mL in the general population (Steenland et al., 2009a). Importantly, available evidence indicates that continued exposure to even relatively lower drinking water concentrations, which are more widespread (Section 3 above), can also substantially increase total human exposure, as indicated by PFOA serum levels.

Chronic human drinking water exposure has been shown to increase the serum PFOA concentration, on average, by about 100-fold the drinking water concentration, with a greater average increase in the serum levels of young children (discussed in detail in Section 5.1). Thus, an approximate 100:1 ratio exists between serum level increase and drinking water concentration. Based on this ratio, drinking water concentrations of 1 ng/L, 10 ng/L, 40 ng/L, 100 ng/L, and 400 ng/L (consumed chronically) are expected to increase serum levels, on average, by about 0.1 ng/mL, 1 ng/mL, 4 ng/mL, 10 ng/mL, and 40 ng/mL, respectively. Assuming that the contribution of drinking water to the U.S. general population mean serum level of about 4 ng/mL is negligible, exposure to these drinking water concentrations is thus estimated to increase serum levels, on average, by 2.5%, 25%, 100%, 250% and 1000%, respectively, to about 4.1 ng/mL, 5 ng/mL, 8 ng/mL, 14 ng/mL, and 44 ng/mL. Increases of these magnitudes are potentially important because serum levels within and below this range are positively associated with multiple health endpoints in humans (Section 6.1).

Based on the above, drinking water concentrations of 1 ng/L, 10 ng/L, 40 ng/L, 100 ng/L, and 400 ng/L are predicted to contribute about 2.4%, 20%, 50%, 71%, and 91% of total exposure, respectively, in populations with a background serum level of 4 ng/mL from non-drinking water sources. In other locations where general population background levels are below 4 ng/mL, the contribution from a given drinking water concentration will represent a larger percentage of total exposure.

5. Toxicokinetics

PFOA is chemically non-reactive and is thus not metabolized. It persists in humans with a half-life of several years (Table 1; Olsen et al., 2007; Bartell et al., 2010a; Brede et al., 2010; Seals et al., 2011) in contrast to other common organic drinking water contaminants such as tetrachloroethylene, benzene, and methyl tertiary butyl ether (MTBE), which are much more rapidly excreted (Post et al., 2011).

PFOA is essentially completely absorbed after oral exposure (Kemper, 2003; Hundley et al., 2006; Lau et al., 2007), and is also absorbed dermally (Kennedy, 1985; Fairley et al., 2007; Franko et al., 2012) and by inhalation of the dust (Kennedy et al., 1986).

In animal studies, PFOA distributes primarily to the liver and serum, followed by the kidney, with lower concentrations in other organs (Vanden Heuvel et al., 1991; Kemper, 2003; Hundley et al., 2006). In the serum, it is almost totally bound to albumin and other proteins (SRI, 2003; Han et al., 2003). Unlike most other persistent bioaccumulative organic compounds, PFOA does not distribute to fat (Vanden Heuvel et al., 1991; Hundley et al., 2006).

PFOA is excreted in the urine and the feces (Hundley et al., 2006), and is believed to undergo enterohepatic circulation (Kudo and Kawashima, 2003; Johnson et al., 1984).

The half-life varies greatly among species, and between genders in some species (Hundley et al., 2006, Lau et al., 2007; Table 1), due to differences in renal clearance rates. For example, both genders of mice eliminate PFOA slowly, in contrast to the rapid elimination seen in both male and female rabbits. Female, but not male, rats excrete PFOA very quickly, while the opposite gender-specific excretion pattern occurs in hamsters (Hundley et al., 2006). These excretion rates are controlled by organic anion transporters (OATs) responsible for the active transport (secretion or reabsorption) of many organic anions, including endogenous substances and xenobiotics, across membranes in the kidney and other organs (Han et al., 2012; Weaver et al., 2010).

The limited data that are available on isomer-specific kinetics suggest greater retention of some isomers (Loveless et al., 2006; Benskin et al. 2009; De Silva et al., 2009b). After equivalent doses to rats, serum levels of branched PFOA were lower than for linear PFOA. After subchronic administration to rats, most branched isomers were eliminated more quickly than linear PFOA, although two minor unidentified branched isomers were more persistent than linear PFOA (De Silva et al., 2009b).

The human half-life does not differ in males and females and was estimated as 3.8 years in retired workers (Olsen et al., 2007), 2.3 years in a more heterogeneous group of U.S. adults one year after ending exposure to contaminated drinking water (Bartell et al.,, 2010a), and 3.25 years (range 1.03–14.67 years) in 138 German subjects 2 years after stopping exposure to contaminated

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Table 1
Serum/plasma elimination $T_{1/2}$ of PFOA (updated from Lau et al., 2007).

Species	Females	Males	References
Rat	2–4 h	4–6 days	Johnson et al. (1979); Kemper and Jepson (2003)
Mouse	17 days	19 days	Lau et al. (2005)
Rabbit	7 h	5.5 h	Hundley et al. (2006)
Dog	8–13 days	20–30 days	Hanhijarvi et al. (1988)
Monkey	30 days	21 days	Butenhoff et al. (2004a)
Human (males and females combined)	3.8 years (retired workers)		Olsen et al. (2007)
	2.3 years (adults after cessation of exposure from contaminated drinking water)		Bartell et al. (2010a)
	3.3 years (average of men, women, children after cessation of exposure from contaminated drinking water)		Brede et al. (2010)
	Adults and children after cessation of exposure to contaminated drinking water: Highly exposed group: 2.9 years (initial 4 years post-exposure); 10.1 years (> 4 years post-exposure). Less exposed group: 8.5 years (initial 9 years post-exposure); no apparent decline (> 9 years post-exposure).		Seals et al. (2011)

drinking water (Brede et al., 2010). The reason(s) for the inter-individual variability in half-life are not known, but could be due to differences in renal transport by OATs. Serum levels decreased more slowly during the second year of follow-up of the U.S. study group (Bartell et al., 2010b), suggesting either ongoing exposures from sources other than drinking water or that kinetics do not follow first-order elimination.

Because of the differences in renal excretion rates and half-lives discussed above, serum concentrations resulting from a given administered dose vary greatly among species and/or between males and females of the same species. Therefore, comparison between animal species or genders or between experimental animals and humans is most appropriately made on the basis of internal dose, as indicated by serum level, rather than administered dose (USEPA, 2006; Post et al., 2009a; Tardiff et al., 2009). A similar approach based on interspecies comparison on a body burden basis is used for other chemicals for which the half-life varies greatly between species, such as 2,3,7,8-TCDD (USEPA, 2010b).

Because PFOA is excreted rapidly ($t_{1/2}$ = 2–4 h) in female rats, it does not reach steady-state after continued once-daily dosing, and fetal exposures in rats from a given dose are much lower than in other species. For this reason, the rat is not an appropriate model for studying potential human developmental effects of PFOA. In contrast, PFOA persists in both genders of mice with a half-life of 17–19 days and reaches steady state with continued dosing. Thus, the mouse is a more suitable model and has been used in many recent developmental studies, such as Lau et al. (2006) and subsequent studies (Section 6.2.1.4).

At higher doses, the kinetics of PFOA in rodents and primates (Griffith and Long, 1980; Ylinen et al., 1990; Mylchreest, 2003; Butenhoff et al., 2004a; Perkins et al., 2004; Loveless et al., 2006; Lau et al., 2006; Das et al., 2010) are not consistent with one-compartment or simple first-order models (Andersen et al., 2006; Clewell, 2009). Serum levels did not increase proportionally with increasing dose, except at lower doses in some studies. Additionally, steady-state was reached more rapidly at high doses than the length of time predicted by classical kinetics (4–5 half-lives).

However, at lower doses closer to those relevant to human environmental exposures, kinetics are consistent with first order processes, and serum levels are proportional to administered dose (Clewell, 2009; Lou et al., 2009; Loveless et al., 2006; Das et al., 2010). Available data indicate that serum levels in mice that would result from doses below the administered range can be estimated by linear extrapolation from data from doses of 1 mg/kg/day or lower. The kinetics are consistent with the saturation of OATs responsible for renal reabsorption at high doses, resulting in a higher excretion rate at high doses than at low doses (Andersen et al., 2006; Clewell, 2009).

Consistent with observations in animals given low doses, the relationship between external dose and internal dose (serum level) is linear in humans with environmental exposures to PFOA, such as from contaminated drinking water (Clewell, 2009). However, non-linear kinetics, as seen in animals at higher doses, may occur at higher (occupational) human exposures (Clewell, 2009).

Recently, Seals et al. (2011) reported that elimination rates differed between former residents of two of the communities with contaminated drinking water studied by Bartell et al. (2010a,b). The half-life in former residents of the community with higher initial serum due to higher levels of PFOA in drinking water was estimated at 2.9 years during the first 4 years after exposure ceased and 10.1 years subsequently, while in former residents of the community with lower initial serum levels (due to previous exposure to lower drinking water PFOA levels), the half-life was 8.5 years for the initial 9 years, with no apparent decline in serum levels thereafter. These data suggest that PFOA elimination is biphasic and dependent on serum concentration.

5.1. Relationship between drinking water concentration and serum levels

In communities with drinking water supplies contaminated by PFOA, mean and median serum PFOA levels are elevated above means and medians in the general population (Section 4.2.1). Within such a population using the same source of drinking water, variations in serum PFOA levels arise from interindividual differences in daily water consumption rates (mL/kg/day) and toxicokinetics. As discussed below, data from several communities with drinking water contamination and approaches based on pharmacokinetic modeling indicate that chronic human exposure to PFOA in drinking water increases serum levels, on average, by about 100-fold times the drinking water concentration.

Emmett et al. (2006) reported a median ratio of 105:1 (25th–75th percentile range, 62:1–162:1) between the average PFOA concentration in serum (371 ng/mL) and drinking water (3550 ng/L) in 282 residents of Little Hocking, Ohio, age six years and older, after exposure of at least two years, with a higher median ratio in young children. This approximate 100:1 serum:drinking water ratio was confirmed in communities with lower drinking water concentrations (Post et al., 2009a) based on data from approximately 70,000 residents of Little Hocking and five other Ohio and West Virginia water districts, when background serum levels found in the general population from non-water sources of exposure are taken into account. Drinking water levels in four of these districts were in the range of about 60 ng/L to 400 ng/L, while levels were higher in a fifth district and Little Hocking (Anderson-Mahoney et al., 2008).

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This approximate 100:1 ratio is supported by data from several other studies. In users of contaminated private wells with mean and maximum PFOA levels of 200 ng/L and 13,300 ng/L in the Ohio/West Virginia region discussed above (Hoffman et al., 2011), the estimated ratio was 141:1 (95% CI: 135:1–148:1) based on regression modeling, and 114:1 based on a one-compartment pharmacokinetic model. The 100:1 ratio is also consistent with observations in 98 Minnesota residents tested 34 months after exposure to contaminated drinking water ended (MDH, 2009), if the expected post-exposure decline in serum levels is considered. The observed ratio of approximately 100:1 is also in agreement with a one-compartment model of Harada et al. (2005), as discussed in Post et al., (2009b).

A lower serum:drinking water ratio of approximately 50:1 was observed in a German community whose drinking water source was contaminated with PFOA and other PFCs (Hölzer et al., 2008). Possible reasons for this difference are the use of bottled water by some participants who were aware of the contamination for up to 6 months before their blood was sampled, uncertainty about the duration and time course of the water contamination, or differences in drinking water consumption patterns between German and U.S. residents.

Clewell (2006, 2009) developed a factor, 0.127 (ng/kg/day)/(ng/mL), which relates intake of PFOA (ng/kg/day) and serum level (ng/mL). The factor is based on pharmacokinetic modeling and was validated with data from the exposed community in Little Hocking, Ohio. Using the USEPA (2004) estimated daily water intake of 17 mL/kg/day, application of this factor predicts a serum:drinking water ratio of 133:1.

5.2. Toxicokinetics relevant to developmental exposures

Developmental exposures to PFOA are important because developmental effects are the most sensitive known endpoints for its toxicity, as discussed in the section on animal toxicology (Section 6.2). After gestational exposure of rodents, PFOA is found in the placenta, amniotic fluid, breast milk, and fetus (Fenton et al., 2009).

PFOA and other PFCs were detected in umbilical cord blood from the general population worldwide, including Baltimore, MD (Apelberg et al., 2007), Ontario, Canada (Monroy et al., 2008), Denmark (Fei et al., 2007), Germany (Midasch et al., 2007), Norway (Gützkow et al., in press), the Faroe Islands (Needham et al., 2011). Australia (Toms et al., 2009), South Africa (Hanssen et al., 2010), Korea (Kim et al., 2011), and Taiwan (Lien et al., 2011). Mean serum (or plasma) levels in these studies ranged from 1.1 ng/mL in Korea (Kim et al., 2011) to 4.4 ng/mL in Taiwan (Lien et al., 2011). No geographic pattern is apparent from this limited dataset, as the levels reported from Africa, Australia, Europe, and North America fell in between the levels in the two Asian studies.

In seven studies in which both maternal and cord blood were analyzed, the mean cord blood serum:maternal serum (or plasma) ratio ranged from 0.68:1 to 1.26:1, and the mean ratio was less than 1:1 in all but one study. However, cord:maternal serum (or plasma) ratios for some individual neonate-maternal pairs within these studies were greater than 1:1. Since umbilical cord serum (or plasma) is reflective of neonatal serum (or plasma), these data indicate that serum (or plasma) levels are generally similar in the neonate and the mother. Based on a weighted average of published data, Shin et al. (2011) assumed a newborn:maternal serum ratio of 0.785:1 for the purposes of retrospective exposure modeling.

Beesoon et al. (2011) recently reported that isomer profiles for PFOA and other PFCs differ in maternal and cord serum within an infant–mother pair and concluded that most branched isomers cross the placenta more efficiently than the linear forms.

PFOA was also detected in human breast milk worldwide (reviewed by Liu et al., 2010; White et al, 2011a), including Massachusetts (Tao et al., 2008a), Japan (Tao et al., 2008b), China (So et al., 2006; Liu et al., 2010), Korea (Kim et al., 2011), Belgium (Roosens et al., 2010), Spain (Llorca et al., 2010), Norway (Haug et al., 2011; Thomsen et al., 2010), and Sweden (Sundström et al., 2011). Levels in breast milk were generally similar in studies from different parts of the world. In studies using sensitive analytical methods enabling detection of lower concentrations, median PFOA levels were 0.036 ng/mL (Massachusetts; Tao et al., 2008a), 0.067 ng/mL (Japan; Tao et al., 2008b), and 0.046 ng/mL (China; Liu et al., 2010), while it was not detected or was infrequently found in breast milk in some other studies which had higher detection limits (Fromme et al., 2010; von Ehrenstein et al., 2009). Levels above 0.04 ng/mL (40 ng/L) were frequently found, with some detections exceeding 1 ng/mL (for example, in Belgium (Roosens et al., 2010)).

Breast milk concentrations were reported to be about 1% of mean general population serum levels by Tao et al. (2008a), and to be 2.5% and 9% of median maternal serum levels by Kim et al. (2011) and Liu et al. (2011), respectively. These data suggest a breast milk:serum ratio of about 1:100 to 1:11. Factors which may affect the concentration of PFOA and other PFCs in breast milk include whether the mother has previously nursed other infants and how long after birth the sample is taken (Tao et al., 2008a; Haug et al., 2011; Thomsen et al., 2010). Thomsen et al. (2010) found that average breast milk concentrations decreased by about 7.7% per month, or about 94% during the first year of breast feeding, presumably due to decreased maternal body burden resulting from excretion into breast milk.

Notably, breast milk concentrations were much higher in both the rural and urban samples in Shanghai (urban mean, 0.616 ng/mL; rural mean, 0.814 ng/mL) than in 12 other Chinese provinces (mean, 0.046 ng/mL). Maternal exposures are likely higher in Shanghai than in the other areas sampled because higher levels of PFOA occur in Shanghai drinking water and surface water and many fluorochemical manufacturing plants are located there (Liu et al., 2010).

Based on a maternal breast milk:serum ratio of 1:100 or greater (Tao et al., 2008a; Kim et al., 2011; Liu et al., 2011) and a 100:1 or greater serum:drinking water ratio, the PFOA concentration in breast milk is expected to be similar to or greater than that in the maternal drinking water source. However, fluid consumption on a body weight basis is much higher in infants than in adults. During the first post-partum month, when PFOA levels in breast milk are highest (Thomsen et al., 2010), mean breast milk consumption is 150 mL/kg/day (USEPA, 2008), about 8-fold higher than the mean drinking water consumption in lactating women, 26 mL/kg/day (USEPA, 2004). Thus, assuming a similar half-life for PFOA in mothers and infants, exposure of a nursing mother to PFOA in drinking water results in a higher PFOA intake on a body weight basis and a higher body burden (serum level) in the breast-fed infant than in the mother herself.

Similar exposures would occur in infants fed powdered or concentrated formula prepared with drinking water contaminated with PFOA. For example, the 75th percentile water ingestion rate for infants 1–3 months of age is 151 mL/kg/day (USEPA, 2008). As is the case for the breast-fed infant, exposure to infants who drink formula prepared with contaminated water is expected to be greater than adults using the same water source. Although breast milk or formula consumption on a body weight basis decreases as the infant gets older, it remains much higher than adult water consumption throughout infancy.

The conclusion that exposure from a given drinking water concentration is greater in infants than in adults is supported by the observation that serum levels in nursing infants are higher than

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in their mothers (Fromme et al., 2010). Maternal and cord blood serum PFOA concentrations were studied in 53 German mothers at birth and in their breast-fed infants. Average body burdens, as indicated by serum levels, were increased from birth to 6 months by exposure through breast milk. Levels declined between 6 months and 19 months, a time point at which breast feeding had stopped or was decreased, but remained higher at 19 months than at birth (Fig. 3). Fenton et al. (2009) also observed a similar pattern in mouse pups, with PFOA body burdens increasing from gestation day (GD) 18 to postnatal day (PND) 8, and decreasing between PND 8 and 18 when the intake of milk has decreased.

Serum concentrations were higher in children younger than 6 years than in adults who were exposed to 3550 ng/L PFOA in drinking water in Little Hocking, Ohio (Emmett et al., 2006), and were higher in children (age 0–9 years) than in those 10–49 years old in the larger C8 Health Study population (Section 6.1) who were exposed to varying drinking water concentrations (>50 ng/L to over 3000 ng/L; Steenland et al., 2009a). More recently, Shin et al. (2011) estimated a median 1-year-old:maternal serum ratio of 1.27:1 from data on 40 child–mother pairs in the C8 Health Study. Serum levels in children up to age 12 were higher than in their mothers in this population; in those up to age 5, mean levels were 44% higher than maternal levels (Mondal et al., in press). The potential for elevated exposure in infants and young children is of particular relevance to potential health effects because PFOA causes toxicity in neonatal mice exposed only through lactation (Section 6.2.1.4).

6. Health effects

Much of the information on health effects of PFOA in humans and animals is recent. Kennedy et al. (2004) and Lau et al. (2007) provide comprehensive reviews of the toxicology literature for PFOA up to the times at which they were written. Subsequent to the recent review of the epidemiologic literature by Steenland et al. (2010b), many additional human studies have become available at a rapid pace.

6.1. Human epidemiology

PFOA exposure, as indicated by serum levels, has been associated with multiple endpoints, including some considered adverse, in epidemiology studies of the general population, communities with contaminated drinking water, and workers,

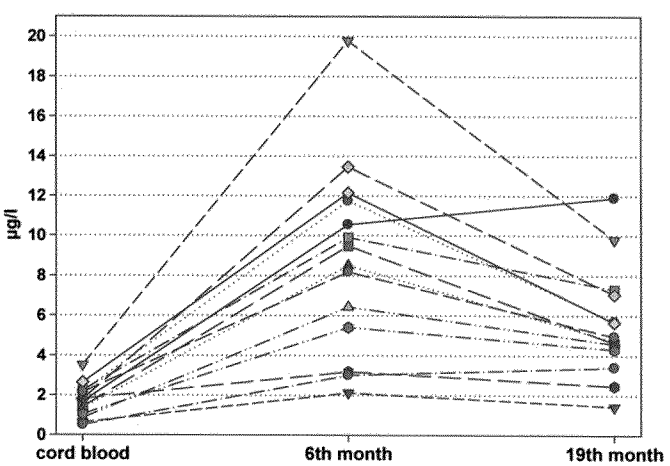

Fig. 3. PFOA concentration in breast-fed German infants in cord blood at birth and in blood collected at around 6 and 19 months after birth, $n=14$ (Fromme et al., 2010).

with consistency for some endpoints in these three types of study populations. Overt toxicity or mortality has not been reported in humans after accidental or intentional acute exposure to concentrations of PFOA higher than those normally encountered in the workplace (ATSDR, 2009).

Data on endpoints that are associated with PFOA exposure in more than one study are summarized in Table 2; data on additional associations reported in a single study are not shown in this table. The studies included in Table 2 reported analyses of mortality or incidence by standardized mortality ratio (SMR), standardized incidence ratio (SIR), hazard ratio (HR), and/or rate ratio or relative rate (RR) and analyses of clinical chemistry by analysis of variance (ANOVA) and/or multivariate linear, logistic, mixed effects or generalized estimating equations regression slopes. In some studies, odds ratios (ORs) were also calculated for parameters with values outside of the clinical reference levels. The SMR and SIR are the ratios of observed deaths or occurrences, respectively, among an exposed population versus the expected number of deaths or occurrences based on an indirect comparison population; these are generally based on rates in an entire country or state, but also can be an internal comparison within a large cohort. The RR is the ratio of rates (e.g., number of cases per 100,000 people per year), generally comparing the rate of an occurrence among those exposed to a risk factor of interest versus the rate among those not exposed. It is generally used in prospective, cross-sectional and ecologic level studies. The HR is generally used for internal comparison within a cohort similar to a rate ratio, but is determined by a proportional hazards statistical method which calculates the change in the hazard over time and includes the movement of subjects into and out of those at risk during the time frame of the analysis. The OR is the ratio of the odds of an event occurring in an exposed or experimental group to the odds of it occurring in a reference group. The RR and OR will tend to converge in large studies.

As is the case for many epidemiological studies, causality cannot be definitively established in these studies, largely because of their cross-sectional design, but the consistency of findings strongly suggests a causal relationship for some endpoints. Some effects in animals are similar to associations seen in humans, while for other effects such as lipid metabolism, humans and animals appear to react differently. Notably, the dose response curve for associations with several endpoints appears steepest at the lower exposure levels, including the range of serum levels found in the general population, with no apparent threshold for some endpoints.

Epidemiological information from populations with contaminated drinking water is available from the C8 Health Study, a community health study of approximately 70,000 Ohio and West Virginia residents with at least one year of exposure to drinking water contaminated with PFOA at ≥ 50 ng/L to over 3000 ng/L (West Virginia University School of Medicine, 2009; Frisbee et al., 2009). Some participants also had occupational exposure. This study is unique because of its large size, the wide range of exposure levels, the number of parameters studied, and because the data on serum concentrations of PFOA provide crucial information on the relationships between external dose (exposure through drinking water), internal dose (serum level), and biological changes. The median overall serum level for all participants was 28.2 ng/mL, and the median in the highest decile was 482 ng/mL, while the lower two deciles coincide with exposures prevalent in the general population (≤ 10 ng/mL). Additional studies, including prospective studies, are ongoing in this population.

In the C8 Study Health Study population, many health endpoints have been significantly associated with serum PFOA levels, after adjustment for potential confounders. These include elevated cholesterol and other serum lipid parameters in adults and

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Table 2
Summary of health endpoints associated with PFOA in multiple human studies.

Endpoints	Workplace					General Population		
	3M—Decatur, AL, USA (PFOA and PFOS)	3M—Cottage Grove, MN, USA	3M—Antwerp, Netherlands (PFOA and PFOS)	DuPont—Parkersburg, WV, USA	Miteni—Italy	C8 Health—Study OH-WV, USA communities with contaminated drinking water near DuPont plant	NHANES—USA	Danish Cancer Registry
Cancer								
Bladder	+ [a] [b]	[c]	NR	+ [d] [e]	NR	NR	NR	[f]
Kidney	+ [a]	[c]	NR	+ [d] ± [e] + [g]	NR	NR	NR	[f]
Prostate	± [h]	± [c]	NR	[d] [e]	NR	NR	NR	[f]
Cardio- and cerebro-vascular								
↑Serum Cholesterol	± [i]	[i]	[i]	+[j], +[k]	+[l]	+[m]	+[n]	NR
↑Serum Uric Acid	NR	NR	NR	+ [j]	+[l]	+[o]	+[p]	NR
Diabetes	± [h]	± [c]	NR	± [e]	NR	[q]	[r] [s] [t]	NR
Hepatic								
↑Serum enzymes	ALT +[i] GGT+ [i] AST [i] AP +[i]	ALT [i] GGT – [i] AST ±[i] AP [i]	ALT [i] GGT – [i] AST [i] AP –[i]	ALT ± [j], [k] GGT + [j], [k] AST ± [j], + [k] AP – [j]	ALT +[u] GGT+ [u] AST [u] AP + [u]	ALT + [v] GGT ± [v]	ALT +[w] GGT + [w]	NR
↓Serum bilirubin	+[i]	[i]	[i]	[j], + [k]	+[l]	+ [v]	[w]	NR
Renal								
↑ Serum calcium, iron, potassium	NR	NR	NR	+ [j]	NR	± [x]	NR	NR
Thyroid								
Thyroid disease	[h]	NR	NR	NR	NR	+[y] +[z]	+ [t]	NR
Thyroid hormone	+[aa]	+[aa]	+[aa]	NR	NR[bb]	[y] +[cc]	NR	NR
Reproductive hormones								
Estradiol	NR	[dd]	NR	+↑ ♂ [j]	NR	± ↓ ♀ [x]	NR	NR
Testosterone	NR	[dd]	NR	+↑ ♂[j]	NR	± ↓boys [x]	NR	NR

Symbols and abbreviations: +, $p < 0.05$; ±, marginal statistical significance ($p = 0.05$–0.099 unless otherwise noted); , $p > 0.10$; NR, not reported.

[a] Based on SMR and category/duration of job exposure (Alexander et al., 2003); bladder cancer SMR = 16.1 (95% CI 3.3, 47) and kidney cancer SMR = 5.1 (95% CI 1.05,15) among those who worked for at least 1 year in a high PFOS exposure job. Workers' PFOA exposure was highly elevated compared to comparison group, but analysis by PFOA exposure level was not reported.

[b] Based on SIR and category/duration of job exposure to PFOS (Alexander and Olsen, 2007). Workers' PFOA exposure was highly elevated compared to comparison group, but analysis by PFOA exposure level was not reported.

[c] Based on HR (Lundin et al., 2009); bladder cancer HR = 1.7 (95% CI 0.4,7.8) among workers with > 1 year cumulative high exposure equivalent, limited by small numbers of bladder cancer deaths; prostate cancer and diabetes HRs in the combined moderate and high exposure category were 3.2 (95% CI 1.0, 10) and 3.4 (95% CI 1.3, 9.3), respectively. No diabetes deaths in high exposure group, which was limited by small numbers.

[d] Based on company-wide SIRs for whole facility (Leonard et al., 2003).

[e] Based on SMRs for whole facility compared to US and WV in general, and to DuPont workers in same geographical region (Leonard et al., 2008). SMRs for kidney cancer and diabetes compared to other DuPont workers in same geographical region were 1.8 (95% CI 0.93, 3.2) and 2.0 (95% CI 1.2, 3.0), respectively. SMRs compared to US and WV populations were less significant, 1.6 (95% CI, 0.80, 2.7), for kidney cancer, and were not significant (< 1.0) for diabetes.

[f] Based on RR (Eriksen et al., 2009), for PFOS, the RR for prostate cancer in the highest quartile of exposure was 1.4 (95% CI, 0.99–1.93).

[g] Based on RR for worker mortality versus serum PFOA (C8 Science Panel, 2011a).

[h] Based on health claims RR versus PFOS exposure category (Olsen et al., 2004). Comparison of long-term (> 10 years) PFC workers versus non-PFC workers at same facility found an RR = 8.2 (95% CI 0.8, > 100) for prostate cancer and an RR = 1.3 (95% CI 0.9, 2.0) for diabetes. PFC workers' exposure to PFOA was also highly elevated compared to comparison group, but analysis by the PFOA exposure level was not reported.

[i] Based on multivariate linear regression of log-transformed variables (Olsen and Zobel, 2007):
Total cholesterol versus serum PFOA among **Decatur** participants, $p = 0.06$, but not associated with serum PFOA among all three 3M facilities combined.
ALT versus serum PFOA among **all three 3M facilities** combined, $p = 0.06$ or 0.40, depending on the regression model.
GGT versus serum PFOA among **all three 3M facilities** combined, $p = 0.05$ or 0.55, depending on the regression model.
AST versus serum PFOA among **Cottage Grove** participants, $p = 0.07$–0.08, depending on the regression model, but not associated with serum PFOA among all three 3M facilities combined.
AP not associated with serum PFOA among **all three 3M facilities** combined.
Total bilirubin versus serum PFOA among **all three 3M facilities** combined, $p = 0.001$ or 0.01, depending on the regression model.

[j] Based on multivariate linear regression in a cross-sectional study (Sakr et al., 2007a); increased ALT and AST versus serum PFOA, $p = 0.071$ and 0.079, respectively, among subjects not taking lipid-lowering medication.

[k] Based on multivariate regression in a longitudinal study (Sakr et al., 2007b).

[l] Based on multiple analyses (Costa et al., 2009) versus serum PFOA.

[m] Based on multivariate regression and trend of increasing ORs of subjects exceeding the clinical standard versus serum PFOA in adults (Steenland et al., 2009b) and children (Frisbee et al., 2010).

[n] Based on multivariate regression (Nelson et al., 2010).

[o] Based on multivariate regression (Steenland et al., 2010a).

[p] Based on multivariate regression (Shankar et al., 2011a).
[q] Based on ORs of self-reported diabetes with or without medical record validation (MacNeil et al., 2009).
[r] Based on homeostatic assessment calculation (Lin et al., 2009).
[s] Based on homeostatic assessment calculation (Nelson et al., 2010).
[t] Based on self-report (Melzer et al., 2010); thyroid disease significant in women and marginally significant ($p=0.073$) in men, based on comparison of 4th quartile for serum PFOA to 1st and 2nd quartiles.
[u] Based on multivariate generalized estimating equations (Costa et al., 2009) versus serum PFOA, cross-sectional study.
[v] ALT was significantly associated by all methods of analysis; GGT was significantly associated by "within water systems" analysis, but not by "between water systems" analysis or by the general logistic analysis of clinically relevant levels. For direct bilirubin, there was an apparent U-shaped dose-response: increasing bilirubin at the low serum PFOA levels and decreasing bilirubin (as found in most occupational studies) at the PFOA serum levels > 40 ng/mL; significantly associated by "between water system" analysis (Gallo et al., in press).
[w] Based on linear regression (Lin et al., 2010).
[x] Based on visual inspection of the graphical data reported by the C8 Health Project (West Virginia University School of Medicine, 2009).
[y] Based on linear regression analysis, PFOA was associated with hypothyroidism, but not thyroid hormone levels, in children < 18 years old (C8 Science Panel, 2011e; Lopez-Espinosa et al., in press).
[z] Based on linear regression analysis, PFOA was associated with hypothyroidism in adult women (C8 Science Panel, 2011f).
[aa] Based on multivariate regression; only reported for all three 3M plants combined (Olsen and Zobel, 2007); statistically significant decrease of free serum T4 and marginally significant increase of serum TSH ($p=0.07$); $p=0.11$ for increased T3.
[bb] Thyroid hormone levels reported only for exposed group in 2007 (Costa et al., 2009).
[cc] Based on multivariate general linear modeling in adults (Knox et al., 2011b); increased serum T4.
[dd] Olsen et al. (1998).

children, including increased risk of clinically defined high cholesterol (Steenland et al., 2009b; Frisbee et al., 2010), increased risk of elevated uric acid in adults, including clinically defined hyperuricemia (Steenland et al., 2010a), elevation of the liver enzyme alanine aminotransferase (ALT; Gallo et al., in press), changes in several indicators of inflammatory and immune response (C8 Science Panel, 2009), delayed puberty in girls (Lopez-Espinosa et al., 2011), early menopause (Knox et al., 2011a), increased thyroxine (T4) and decreased triiodothyronine (T3) uptake (binding of free T3 to a resin added to serum; Knox et al., 2011b), thyroid disease in women (C8 Science Panel, 2011f), and osteoarthritis (Innes et al., 2011). Thyroid disease in children, for which the number of cases was small, was associated with serum PFOA with borderline significance (C8 Science Panel, 2011e; Lopez-Espinosa et al., in press). Forthcoming studies will evaluate other endpoints, including cancer incidence, in this population.

General population cross-sectional studies based on NHANES and other data found associations with several endpoints at serum levels of 10 ng/mL or below, some of which are consistent with findings in the C8 Health Study. Findings include increased serum cholesterol (Nelson et al., 2009) and uric acid (Shankar et al., 2011a), increased incidence of thyroid disease (Melzer et al., 2010), increased serum liver enzymes (Lin et al., 2010), decreased renal glomerular filtration (Shankar et al., 2011b), and effects on sperm parameters (Joensen et al., 2009).

Maternal serum PFOA was associated with decreased fertility as measured by time to pregnancy in Denmark (Fei et al., 2009); this association was not confirmed in a subsequent Danish prospective study of couples attempting to conceive their first child (Vestergaard et al., 2012). In a recent study in a Norwegian population, increased time to pregnancy was associated with maternal serum PFOA in parous, but not nulliparous, women (Whitworth et al., 2012). Interactions among factors that are potentially relevant to these findings, including serum PFOA, parity, past fertility, and time to pregnancy, are discussed by Fei et al. (2012).

An association with increased incidence of attention deficit hyperactivity disorder (ADHD) in adolescents in NHANES (Hoffman et al., 2010) is not consistent with negative findings in the C8 Health Study (C8 Science Panel, 2011b; Stein and Savitz, 2011), and no association was found between prenatal exposure and behavioral or motor coordination problems in 7-year-old Danish children (Fei and Olsen, 2011).

Increased serum IgE was associated with cord blood PFOA in 2-year-old Taiwanese boys (Wang et al., 2011b), while decreased cord blood IgE in newborn Japanese girls was associated with maternal serum PFOA (Okada et al., 2012). In the latter study, maternal PFOA was not associated with allergies and infectious disease at 18 months of age. Grandjean et al. (2012) recently reported a reduced antibody response to tetanus and diphtheria booster immunizations at ages 5 and 7 with increasing serum PFOA and PFOS in children from the Faroe Islands. A twofold increase in serum PFOA and PFOS was associated with an approximately 2-fold reduction of tetanus and diphtheria antibodies, and with an approximate 2- and 4-fold increased risk, respectively, for tetanus and diphtheria antibody levels falling below clinically protective levels.

Finally, body mass index (BMI) and waist circumference, including increased risk of being overweight/obese and having a waist circumference defined as high, in 20-year-old Danish females were associated in a dose-related fashion with prenatal exposure to PFOA, as assessed by levels in their mothers' serum. In these 20-year-old women, insulin and leptin were increased, and adiponectin was decreased, with increasing maternal PFOA (Halldorsson et al., in press).

Associations for several endpoints in the C8 Health Study, including cholesterol, uric acid, and the liver enzyme ALT, exhibit a steep dose-response curve in the lower deciles of PFOA exposure, consistent with findings at similar serum PFOA levels in general population studies. Notably, the median serum levels in the first and second deciles in the C8 Health Study, 6 ng/mL and 9.8 ng/mL, coincide with the 75th and 95th percentiles in the U.S. general population (Kato et al., 2011). For these endpoints, no threshold is apparent in the dose-response; if a threshold exists, it is below the median serum concentration in the first decile. For some of these effects, such as cholesterol and uric acid, there is an apparent plateau at higher serum levels above 40 ng/mL (Steenland et al., 2010b; Fig. 3).

In addition, several population-based reproductive outcome studies based on maternal and/or umbilical cord blood data in the U.S., Canada, Denmark, and Japan are available. As noted by Olsen et al. (2009), analyses with more data on potential confounders or maternal/cord serum PFOA levels, including the Apelberg et al. (2007) study in Baltimore, the Danish National Birth Cohort (Fei et al., 2007; 2008) studies, and a Japanese (Washino et al., 2009) study, generally found statistically significant or marginally significant inverse associations between birth weight or other measures of fetal growth and PFOA and/or other PFCs. Hamm et al. (2010) also observed an inverse relationship with birth weight as a continuous variable, but a positive relationship when

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analyzing birth weight tertiles. In the Danish population (Andersen et al., 2010), decreased growth parameters at 5 and 12 months were also associated with increasing maternal serum PFOA and PFOS, particularly in boys. In contrast, studies with less data on confounders (Grice et al., 2007) and those based on external exposure (e.g. drinking water PFC concentration) rather than internal dose (serum PFC data), such as Nolan et al. (2009), did not find statistically significant associations. Monroy et al., (2008) reported results as ng/mL serum PFOA per gram birth weight, so it is difficult to interpret their statistical analysis.

The C8 Science Panel reported no association between low birth weight at term and estimated PFOA serum levels during pregnancy in approximately 12,000 pregnancies in the C8 Health Study population from 1990 to 2005 (C8 Science Panel, 2011c). Similar findings were reported for a smaller number of pregnancies in this population from 2000 to 2006 by Stein et al. (2009) and in a recent prospective study of about 1500 births in this population from 2005 to 2010 (C8 Science Panel, 2011g). It should be noted that the endpoint evaluated by the C8 Science Panel (2011c) and Stein et al. (2009) was clinically defined low birth weight, while change in birth weight as a continuous variable was the endpoint evaluated in the other studies mentioned above (C8 Science Panel, 2011h). More recently, the C8 Science Panel (2011g, 2011h) and Savitz et al. (2012b) noted a small association of reduced birth weight with increasing serum PFOA. Thus, the findings in the C8 study population do not necessarily contradict the results of the other studies.

It has been suggested that associations of decreased birth weight with increased serum PFOA within the narrow exposure range of the general population may be due to greater maternal plasma volume, and thus greater dilution of serum PFOA, in women who deliver larger infants (Longnecker, 2010). However, this phenomenon may not explain such associations when observed over the wider range of PFOA serum levels arising from exposure to environmental contamination, such as in the C8 Health Study population.

Increased risk of preeclampsia, a more severe form of pregnancy-induced hypertension, was associated with maternal serum PFOA in the C8 population (Stein et al., 2009; C8 Science Panel, 2011c; Savitz et al., 2012a) and was statistically significant in the latter larger study. This study included 11,737 pregnancies between 1990 and 2005 for which exposure was assigned based on exposure reconstruction models that linked data on industrial discharge of PFOA, environmental transport of PFOA to drinking water supplies, pharmacokinetic modeling, and residential history. Increased risk of pregnancy-induced hypertension was also associated with PFOA exposure in the prospective study of pregnancies in this population mentioned above (C8 Science Panel, 2011g). Based on these data, the C8 Science Panel concluded that there is a probable link between exposure to PFOA and pregnancy-induced hypertension (C8 Science Panel, 2011i). Frank eclampsia was also marginally statistically significant (unadjusted OR, 7.0; 95% CI,1.0-50) among mothers residing within the Little Hocking (Ohio) Water Association service area in a small zip code-based study (Nolan et al., 2010). Miscarriage/stillbirth and birth defects were not significantly associated with PFOA exposure in the prospective study of the C8 population (C8 Science Panel, 2011g).

Associations of occupational exposures with several diseases and clinical endpoints are also summarized in Table 2; as shown, workers in some of the facilities studied were exposed to both PFOA and PFOS. Increased cholesterol and uric acid, also seen in the C8 Health Study and the general population, are considered to be risk factors for cardiovascular disease (Steenland et al., 2009b, 2010a). Increases in these two serum parameters are consistent with evidence in one or more of the occupational studies of increased mortality from hypertension (not statistically significant due to small numbers in both studies; Lundin and Alexander, 2007; Leonard et al., 2008), ischemic heart disease (Sakr et al., 2009), stroke (Lundin et al., 2009), and diabetes (Table 2). The enzyme ALT, a marker of hepatocellular damage, was also increased in all three types of study populations. The occupational studies also showed some consistency of increased cancer mortality and/or incidence, including bladder, kidney and prostate cancer. White blood cell neoplasms (Leonard, 2003; Leonard et al., 2008), thyroid cancer (Leonard et al., 2008), and carcinoid tumors (Morel-Symons et al., 2007) were also increased at one industrial facility. Unfortunately, only one of the studies (Olsen et al., 2004) evaluated hypertension in active workers or retirees. Additional worker morbidity and mortality studies based on retrospective exposure modeling are forthcoming (Woskie et al., in press).

As is often the case for such studies, most of the occupational studies of PFOA have several notable limitations. Many were voluntary and had low participation rates and/or were cross-sectional in design. Mortality and incidence studies at one of the major PFOA production facilities in the U.S., the DuPont Washington Works, did not report analysis based upon exposure (except for the study of ischemic heart disease by Sakr et al., 2009). Exclusion of short-term workers (e.g., <1 yr employment) who may have had high exposures could undercount exposed cases. Many studies relied on death certificate data which often do not provide information on diseases that were not the direct cause of death, such as diabetes or prostate cancer (Bild and Stevenson, 1992). The small proportion of exposed female employees limits the ability to assess specific effects among women. Effects may have been modified by exposures to PFCs other than PFOA or to other chemicals. Finally, the currently available occupational studies were not designed to detect developmental effects that are not manifested until later in life in the offspring of exposed workers.

Serum cholesterol is the endpoint for which the greatest number of epidemiology studies is available. The slope of the serum PFOA versus total cholesterol relationship varied by 2–3 orders of magnitude among the nine studies in which a positive association was found; it was steeper in the general population and in a community with drinking water exposures than in highly exposed workers (Steenland et al., 2010b). The authors state that this finding might be explained if the slope of the exposure–response relationship is steep at low exposures and then flattens out, as in Fig. 4, when some biological pathways become saturated.

Because exposures among the least exposed groups of workers were in the upper ranges of exposures in the C8 Health Study where the plateau is observed, occupational studies of effects for which the dose–response curve exhibits a plateau, such as increased cholesterol and uric acid, may not have had an appropriate comparison

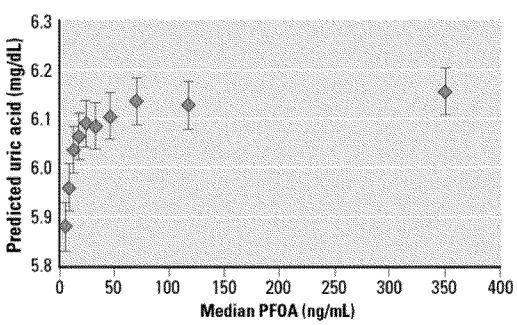

Fig. 4. Serum uric acid with increasing serum PFOA in C8 Health Study participants $\geq$20 years of age. Predicted from regression model for an average participant (Steenland et al., 2010a).

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Table 3
LOAELs and NOAELs identified for toxicity endpoints in experimental animals.

Effect	Study	Endpoint	NOAEL		LOAEL	
			Dose (mg/kg/day)	Serum level (ng/ml)	Dose (mg/kg/day, except as noted)	Serum level (ng/ml)
Hepatic-Adult	Rat 13 week dietary (Perkins et al., 2004)	↑ liver weight, peroxisome proliferation, hepatocyte hypertrophy	0.06	6500	0.64	55,000
Hepatic-Adult	Mouse 14 day gavage (Loveless et al., 2006)	↑ relative liver weight	NA	NA	0.3	13,000 (linear PFOA); 14,000 (branched PFOA)
Hepatic-Adult	Mouse 21 day drinking water (Son et al., 2008)	↑ relative liver weight	NA	NA	0.49	NA
Hepatic-Pup	Mouse developmental gavage (GD 10-17) (Macon et al., 2011)	↑ liver weight	0.1	2300 (PND 1)	1	16,305 (PND 1)
Immune	Mouse 21 day drinking water (Son et al., 2009)	↓ cell number and percentage of mature splenic lymphocytes	NA	NA	0.49	NA
Neurobehavioral	Mouse neonatal gavage (single dose, PND 10) (Johansson et al., 2008)	Behavioral changes at age 4 months	NA	NA	0.58 (single dose)	NA
Neurobehavioral	Mouse dietary throughout gestation (Onischenko et al., 2010)	Behavioral changes in offspring at age 5-8 weeks	NA	NA	0.3	NA
Developmental	Mouse gestational gavage (GD 10-17) (Macon et al., 2011)	Delayed mammary gland development in pups assessed on PND 21	NA	NA	0.01	285 – pup (PND 1)
Developmental	Mouse multi-generation drinking water (White et al., 2011b)	Delayed mammary gland development in F1 pups on PND 22	NA	NA	5000 ng/L in drinking water	21 – pup (PND 22)
Metabolic/ Developmental	Mouse gestational gavage (GD 1-17) (Hines et al., 2009)	Obesity, ↑ insulin, and ↑ leptin in mid-adulthood.	NA	NA	0.01	NA
Reproductive/ Developmental	Immature mouse gavage (PND 18-20) (Dixon et al., in press)	Histopathologic changes in uterus, vagina, cervix; ↑ uterine weight on PND 21.	NA	NA	0.01	NA
Carcinogenicity*	Male rat chronic dietary (Biegel et al., 2001)	Testicular Leydig cell, pancreatic, and liver tumors; 10% incidence	NA	NA	13.6 at 10% tumor incidence	572,000 (Modeled, see USEPA, 2005; Post et al., 2009a)

NA – data not available; GD – gestation day; PND – postnatal day.

* LOAEL/NOAEL approach not applicable for linear low-dose extrapolation of tumor data.

group when comparisons were made within groups of workers within a facility.

Steenland et al. (2009b) reported that serum PFOA levels in the C8 Health Study were similar in individuals who had or had not taken statins (cholesterol-lowering drugs). They state that these results provide some evidence against reverse causality (i.e., increased cholesterol causing increased retention of PFOA), which is a potential issue in studies using cross-sectional data.

Recently, the magnitude of decrease in LDL cholesterol (associated with increased risk of cardiovascular disease) was correlated with the magnitude of decrease in serum PFOA levels in C8 Health Study participants after exposure to contaminated drinking water ceased (C8 Science Panel, 2011j). These results contribute to the weight of evidence for a causal relationship between PFOA exposure and elevations of serum lipids.

6.2. Toxicity in experimental animals

There is a steep dose-response curve for mortality in experimental animals exposed to PFOA. PFOA causes weight loss, hepatic toxicity, effects on lipid metabolism, changes in hormone levels, immune system effects, persistent neurobehavioral effects from a single dose to neonates, tumors of several organs in rats dosed chronically, and several types of developmental effects. Recent studies show that developmental toxicity occurs at lower doses and is a more sensitive endpoint than the long-established hepatic effects. As discussed in Section 5, comparisons between animal species and between humans and animals are most appropriately based on serum levels. Lowest Observed Adverse Effect Levels (LOAEL) and/or No Observed Adverse Effect Levels (NOAEL), expressed as administered dose and as serum level (when available), for several endpoints are shown in Table 3.

6.2.1. Non-tumor effects

6.2.1.1. Hepatic effects. PFOA causes liver enlargement and toxicity in experimental animals including rodents and non-human primates; hepatocellular hypertrophy and necrosis were found in some studies (Butenhoff et al., 2004a; Perkins et al., 2004; Loveless et al., 2006; Son et al., 2008; many other studies reviewed in Kennedy, et al., 2004; Lau et al., 2007; ATSDR, 2009). Chronic exposure also caused hepatic adenomas in rats (Section 6.2.2). Hepatic effects, as indicated by elevated serum liver enzymes, are also associated with PFOA in humans (Section 6.1).

6.2.1.2. Immune system effects. The effects of PFOA and other PFCs on the immune system were recently reviewed by Dewitt et al. (2012). PFOA suppresses the immune system in mice. Effects include

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decreased spleen and thymus weights, decreased thymocyte and splenocyte counts, decreased immunoglobulin response, and changes in specific populations of lymphocytes in the spleen and thymus (Yang et al., 2000; Yang et al., 2002; Dewitt et al., 2008,2009; Loveless et al., 2008; Son et al., 2009). PFOA also caused atrophy of lymphoid follicles in the spleen and in the lymph nodes in rhesus monkeys (Goldenthal, 1978). Little information is available on immune system effects from developmental exposure (Dewitt et al., 2012). Suppression of the immune system observed in animals is consistent with the recent report of decreased antibody response to childhood vaccines with increasing serum PFOA and PFOS (Grandjean et al., 2012).

6.2.1.3. Neurobehavioral effects. Gestational or neonatal exposure to PFOA causes persistent neurobehavioral effects, particularly increased activity, in mice (Table 3; Johansson et al., 2008; Onischenko et al., 2010). Possibly relevant to these behavioral changes, PFOA also increased the levels of four brain proteins important for growth of neurons and synapses (CaMKII, GAP-43, synaptophysin, and tau) in 10-day old mice, a period of rapid brain development (Johansson et al., 2009).

6.2.1.4. Reproductive and developmental effects. Prior to 2006, the reproductive and developmental effects of PFOA had been studied only in rats and rabbits (Gortner, 1981, 1982; York, 2002; Butenhoff et al., 2004b). These species are not suitable as models for human developmental effects due to the very rapid elimination of PFOA in females (Section 5; Table 1). In subsequent studies in mice, a more appropriate species because of the long half-life in females, gestational exposure caused increased maternal liver weight, delayed parturition, full litter resorptions, decreased postnatal survival and growth, delayed ossification and eye opening, and sexual maturation acceleration in males and delay in females (Lau et al., 2006). The LOAEL for maternal and fetal toxicity was 1 mg/kg/day, with no NOAEL identified (Lau et al., 2006), and the dose-response curve was non-monotonic for several endpoints, with greater effects at 1 mg/kg/day than at one or more of the higher dose levels. In cross-fostering studies, some neonatal effects occurred when exposure occurred only during lactation; the magnitude of these effects was greater with exposure during both gestation and lactation, followed by gestation only, with the smallest effects from lactation-only exposure (Wolf et al., 2007).

In recent studies, developmental exposure to a much lower dose of PFOA, 0.01 mg/kg/day, caused several effects in mice; a NOAEL for these effects has not been identified. Gestational exposure (GD 1-17) to this dose caused obesity and increased levels of metabolic hormones (insulin and leptin) in female offspring when they reached adulthood, while the same exposure regimen in early adulthood had no effect on these endpoints (Hines et al., 2009). Similar associations of prenatal PFOA exposure with increased body weight and changes in metabolic hormone levels in 20-year-old women from the general population were recently reported by Halldorsson et al. (in press). Exposure of immature female mice to 0.01 mg/kg/day PFOA for 3 days (PND 18–20) caused histopathologic changes in the female reproductive tract (uterus, vagina, and cervix) and increased uterine weight on PND 21 (Dixon et al., in press). Finally, as discussed in detail below, gestational exposure (GD 10–17) to this same low dose, as well as even lower exposures through drinking water, caused impaired mammary gland development (Macon et al., 2011; White et al., 2011b).

6.2.1.4.1. Effects on mammary gland development. The developing mammary gland is the most sensitive known target for PFOA toxicity in animals, and a NOAEL for these effects has not been identified. The similarities in developmental patterns of the human and rodent mammary gland provide a good model for detecting early effects of developmental exposures to endocrine disrupting chemicals such as bisphenol A, atrazine, and dioxin (Fenton, 2006; Rudel et al., 2011). These changes may be more sensitive endpoints than other endocrine disruption outcomes, and may result in decreased function and/or disease not manifested until later in life (Rudel et al., 2011).

Current information on PFOA's effects on the developing mammary gland was recently reviewed by the Institute of Medicine of the National Academy of Sciences (IOM, 2011). In CD-1 mice, PFOA exposure during critical developmental periods (fetal, neonatal, pregnancy, and lactation) caused delayed mammary gland development in both lactating dams and pups (White et al., 2007; White et al., 2009; Macon et al., 2011; White et al., 2011b), while even a high dose (5 mg/kg/day) did not affect mammary gland development in non-pregnant adult female mice (White et al., 2007). Mammary gland effects occurred at exposures below those that affected other indicators of maternal or pup toxicity such as reproductive endpoints (fetuses/litter, prenatal loss, prenatal survival), body weight, and liver weight in the dosed animals. In cross-fostering studies, delayed mammary gland development resulted from exposure during gestation, lactation, or both, and these effects were considered to be permanent, persisting in exposed offspring until 18 months of age (White et al., 2009). Significant delays in mammary gland development occurred as early as PND 1 in non-gestationally exposed pups that were exposed to breast milk from treated dams for only 12–24 h, and as early as PND 3 in non-gestationally exposed dams that were exposed only through maternal behavior such as ingestion of treated pups' waste and grooming of treated pups (White et al., 2009).

In dams exposed to 5 mg/kg/day, expression of genes for four milk proteins (beta-casein, EGF, alpha-Lac, and LactoF) in mammary gland tissue was also affected by PFOA. For example, peaks in LactoF expression normally seen early and late in lactation were delayed, consistent with the observed structural delays in mammary gland development at these time points (White et al., 2007).

Mammary gland development, as assessed on PND 21 by overall developmental score, number of terminal end buds, and other measures was delayed in a dose-related fashion in CD-1 mouse pups after late gestational exposure (GD 10–17) to doses as low as 0.01 mg/kg/day, with no NOAEL identified (Macon et al., 2011). These effects occurred at PFOA serum levels of 285 ng/mL or below; these levels are lower than the mean serum level (371 ng/mL) in a community exposed to highly contaminated drinking water (Emmett et al., 2006).

In a subsequent multi-generation study of CD-1 mice exposed to 5000 ng/L PFOA in drinking water, mammary gland development was delayed in both F1 dams (PND 22) and F1 female pups (PND 22, 42, and 63) at serum levels relevant to human environmental exposures (White et al., 2011b). Pups were significantly affected at serum levels as low as 21.3 ng/mL on PND 22 (compared to 0.6 ng/mL in controls at this time point). This serum level would be expected in humans with ongoing exposure to drinking water concentrations of approximately 200 ng/L, based on a 100:1 serum:drinking water ratio (Section 5.1). It is below the mean serum level of 28 ng/mL in the six Ohio and West Virginia communities with contaminated drinking water that comprise the C8 Health Study population, and is within about 5-fold of the mean and 2-fold of the 95th percentile serum levels in the U.S. general population (Kato et al., 2011).

As part of this study, a lactational challenge experiment was conducted in F1 dams and their F2 litters on PND 10, the time point at which lactation peaks. Milk production was decreased and time to initiate nursing behavior was increased in F1 dams and their F2 litters (White et al., 2011b). However, these changes were not statistically significant, possibly due to high variability and the small number of animals assessed. Additionally, postnatal

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survival and body weight were not affected in the F2 pups, indicating that the ability of the F1 dams to provide nutritional support was not decreased by exposure to 5000 ng/L in drinking water. The authors note that it is not known whether deficits in lactational function were present, but were compensated for by increased frequency or longer duration of nursing events, since these parameters were not assessed.

Mammary gland development after peripubertal exposure was also studied in two other strains of mice, C57Bl/6 and Balb/C. The number of terminal end buds and number of stimulated terminal ducts, was increased in C57Bl/6 mice at 1 mg/kg/day and 5 mg/kg/day and decreased at 10 mg/kg/day, while in similarly treated Balb/C mice these endpoints were decreased at all doses in a dose-related manner (Yang et al., 2009). In this study, uterine weight relative to body weight was decreased significantly at all doses in a dose-related manner in Balb/C mice, while in C57/Bl6 mice, uterine weight was significantly increased at 1 mg/kg/day and significantly decreased at 10 mg/kg/day. Histological changes such as increased or decreased uterine glandular development were consistent with the changes in relative uterine weight. Age at vaginal opening was delayed significantly at the lower doses in both strains, and vaginal opening did not occur at higher doses.

It should be noted that the stimulation of mammary gland development in C57Bl/6 mice exposed to 5 mg/kg/day by Yang et al. (2009) does not contradict the findings of delayed mammary development in CD-1 mice discussed above, since the strains of mice, the lifestage at exposure, and the doses used differed in these studies. Differences in hormonal control of mammary development between C57Bl/6 mice and other mouse strains (Aupperlee et al., 2009) may be relevant to these results.

6.2.2. Tumor effects

PFOA causes tumors in chronically exposed rats and has been classified as "likely to be carcinogenic to humans" by the USEPA Science Advisory Board (USEPA, 2006). It increased the incidence of testicular Leydig cells adenomas in two chronic rat studies (Sibinski, 1987; Biegel et al., 2001). In the latter study, which included only male animals, the incidence of adenomas of the liver and pancreatic acinar cells were also increased. The incidence of all three tumor types in rats given 300 ppm PFOA in the diet (13.6 mg/kg/day) was about 10% higher than in controls (Biegel et al., 2001). Sibinski (1987) reported an increased incidence of mammary gland fibroadenomas and ovarian tubular hyperplasia (a non-tumor endpoint) in female rats, but subsequent pathology reevaluations (Hardisty et al., 2010; Mann and Frame, 2004) concluded that the incidence of these lesions was not increased by PFOA. PFOA has also been shown to promote liver carcinogenesis in rat initiated with diethylnitrosamine, as well as in a more complex initiating protocol (Abdellatif et al., 1991; Nilsson et al., 1991). As discussed in Section 8, available data indicate that PFOA is not mutagenic.

Non-carcinogenic effects are more sensitive endpoints than tumors, based on the application of standard uncertainty factors for Reference Dose development to NOAELs and LOAELs for non-cancer endpoints and linear low-dose extrapolation to the 10^{-6} risk level for currently available tumor data (Post et al., 2009a). However, no chronic studies have been published from species other than the rat, such as the mouse. Such data would be particularly informative because female rats excrete PFOA very rapidly, in contrast to mice, humans, and other species. Furthermore, exposure in the chronic rat studies started at age 6–7 weeks, and thus did not assess effects which could result from exposures during the critical developmental stages now known to be sensitive periods for PFOA toxicity.

6.2.3. General issue: PFOA Exposure in control groups

A general issue for some of the animal toxicology studies of PFOA is unintended exposure in the untreated control groups. For example, serum levels in control groups from some studies were: cynomologus monkey (Butenhoff et al., 2004a) – 134 ng/mL; rat and mouse (Loveless et al., 2006) – 100–400 ng/mL; mouse (Dewitt et al., 2008) – 25–600 ng/mL. Such exposures in control animals also occur in studies of other ubiquitous environmental contaminants. However, this issue is of particular relevance to PFOA because the dose–response curves for several of the associations in human epidemiology studies appear to be steepest at serum levels below 50 ng/mL. When serum levels in the control groups in animal studies are elevated, the shape of the dose–response curve in the lower ranges of serum levels relevant to human environmental exposures cannot be determined. Thus effects which may occur within this range will not be detected.

7. Benchmark dose modeling of mammary gland development data

Benchmark dose (BMD) modeling is a quantitative approach commonly used to estimate the lower 95% confidence bound on the dose corresponding to the lowest response that is consistent with the observed data (the BMDL). The BMDL is considered to be an estimate of the NOAEL, but is based on the entire dose–response curve for the endpoint of interest, rather than on just the fixed doses administered in the study. USEPA Benchmark Dose Modeling Software 2.1.2 was used to perform BMD modeling of the data on mammary gland development in CD-1 mouse pups exposed to 0.01 mg/kg/day, 0.1 mg/kg/day, or 1 mg/kg/day on GD 10-17 (Macon et al., 2011). These data were selected for BMD modeling because mammary gland development is a sensitive and relevant endpoint for PFOA toxicity, PFOA serum levels were reported, and statistically significant, dose-related effects occurred. Continuous response models were used to obtain the BMD and the BMDL for a 10% change from the mean (the % change typically used as the benchmark response) for two endpoints (decreased mammary gland developmental score and decreased number of terminal end buds) that showed a dose-related decrease at PND 21 over the dose range studied (Table 4). Modeling was based on serum levels at PND 1, since they were higher at this time than at later time points. In this study, the serum level in the control group was 22.6 ng/mL, indicating that some PFOA exposure occurred in these non-dosed animals (Section 6.2.3). The serum level BMD and BMDL values presented in Table 4 were derived using this value from the control group (22.6 ng/mL) as the baseline.

Compared to controls, the developmental score at PND 21 significantly decreased at all three doses; the number of terminal end buds also decreased at all three doses, with significance at the two higher doses. The serum level BMDLs for the two endpoints, 24.9 ng/mL and 22.9 ng/mL (Table 4), are close to the serum level NOAEL of 28.5 ng/mL that would be estimated by applying a standard uncertainty factor of 10 for LOAEL-to-NOAEL extrapolation to the serum level of 285 ng/mL at the LOAEL, 0.01 mg/kg/day (see Table 3). It is likely that the serum level BMD and BMDL would have been lower if the baseline serum level had been lower.

Delayed mammary gland development was also observed on PND 22 in F1 female CD-1 mouse pups at a serum PFOA level of 21.3 ng/mL, compared to controls with a serum level of 0.6 ng/mL (Section 6.2.1.4.1; White et al., 2011b). The data from this multi-generation study, in which exposure was through drinking water, are not amenable to BMD modeling because only one dosage level was administered.

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Table 4
Benchmark dose modeling of serum PFOA data (PND1) for mammary gland developmental effects (PND 21) in CD-1 mouse pups exposed to 0.01, 0.1, or 1 mg/kg/day on GD 10-17 (Macon et al., 2011)[a].

Model	*P*-value for log- likelihood ratio	Akaike information criterion (AIC)	BMD (serum PFOA (ng/mL))	BMDL (serum PFOA (ng/mL))
Decreased mammary gland developmental score				
Hill (non-logged concs.)	0.70	4.28	57.4	28.1
Polynomial - 2nd degree (logged concs.)	0.83	4.39	25.9	24.0
Exponential — model 2 (logged concs.)	**0.87**	**36.86**	**25.7[b]**	**24.7[b]**
Linear (logged concs.)	0.83	6.05	28.0	26.5
Decreased number of terminal end buds				
Hill (non-logged concs.)	0.47	88.43	235.1	78.5
Exponential — model 4 (non-logged concs.)	0.30	88.97	399.8	110.5
Power (non-logged concs.)	0.62	88.15	64.8	23.4
Power (logged concs.)	0.81	87.96	87.2	29.0
Polynomial — 2nd degree (logged concs.)	0.84	87.94	96.6	28.1
Linear (logged concs.)	0.12	89.47	27.0	25.7
Exponential — model 3 (logged concs.)	**0.98**	**87.90**	**25.1[b]**	**22.9[b]**

[a] Results are shown for all models which gave an acceptable visual fit.
[b] BMDs and BMDLs from the models with the lowest AIC statistic for each endpoint.

8. Mode of action

The mode(s) of action (MOA) for PFOA are not fully characterized. PFOA structurally resembles a free fatty acid, and thus may act similarly to a free fatty acid in activating nuclear receptors, binding to transporters and carrier proteins, and interacting with membranes (Butenhoff, 2009). However, it is non-reactive and thus is not a substrate for biochemical reactions involving fatty acids.

PFOA was not mutagenic in several *in vitro* assays in bacterial and mammalian cells, and did not induce micronuclei in mice *in vivo* (reviewed by USEPA, 2005; ATSDR, 2009).

PFOA activates the nuclear receptor, peroxisome proliferator-activated receptor α (PPARα), as well as other nuclear receptors such as CAR (constitutive androstane receptor) and PXR (pregnane X receptor) (Rosen et al., 2008a,b; Elcombe et al., 2010). A number of structurally diverse PPARα activating compounds cause liver tumors in rodents; the human relevance of these rodent liver tumors is subject to debate because of the lower levels and/or lower intrinsic activity of PPARα in human liver (NRC, 2006; Corton, 2010). However, this uncertainty about human relevance does not necessarily apply to non-hepatic effects mediated by PPARα.

PFOA's hepatic effects in rodents are partly PPARα-mediated and partly PPARα-independent (Peters and Gonzalez, 2011), in contrast to the model compound Wyeth 14,643 (WY) which acts solely through PPARα activation. This conclusion is based on liver weight, histopathology, biochemical, and genomic data comparing the effects of PFOA and WY in rats and in PPARα-null (knockout, KO) and wild type (WT) mice (Yang et al., 2000; Wolf et al., 2008, DeWitt et al., 2009, Elcombe et al., 2010, Rosen et al., 2008a,b). Moreover, branched isomers of PFOA were more potent in increasing liver weight than the linear form, but less potent in activating PPARα, indicating that PPARα-independent liver effects occur (Loveless et al., 2006).

Recent studies show that PFOA is hepatotoxic to both WT and PPARα-null KO mice, with similarities and differences in the profile of toxic effects observed in the two strains (Minata et al., 2010; Nakagawa et al., 2011; Filgo et al., 2011). Minata et al. (2010) reported that PFOA caused similar increases in liver weight and increases in the liver enzymes AST and ALT in WT and KO mice, although the histopathology indicates different MOAs for hepatocellular toxicity in the two strains. However, KO mice were much more sensitive to bile duct injury than were WT mice, suggesting that PPARα activity may protect against this effect. Since hepatic PPARα may be weaker in its function and present in lower amounts in humans than in mice, it was suggested that the absence of sufficient PPARα activity in humans may render them susceptible to liver damage from high doses of PFOA (Nakagawa et al., 2011). Preliminary data (Filgo et al., 2011) from 18–month-old WT and PPARα KO mice exposed to PFOA only during gestation suggest that PFOA caused liver adenomas in the PPARα KO mice, but not in the WT mice.

Most PPARα activators such as fibrate drugs decrease cholesterol and lipids in both humans and rodents. In contrast, PFOA decreases serum lipid levels in rodents (e.g., Loveless et al., 2006), but is associated with increased serum lipids in humans. However, unlike other peroxisome proliferators such as fibrates, which do not cause fatty liver, PFOA increased triglyceride, phospholipids, and cholesterol accumulation in liver and induced fatty liver in mice (Kudo and Kawashima, 1997). These observations indicate that PFOA affects lipid metabolism in both humans and rodents differently than other PPARα activators.

Fibrate drugs also reduce C-reactive protein, a liver protein that is a marker for inflammation, in humans through activation of PPARα (Kleemann et al., 2003). Serum PFOA was also significantly associated with a strong downward trend for decreased C-reactive protein in the C8 Health Study (C8 Science Panel, 2009), suggesting that this change might also involve PPARα activation.

The USEPA Science Advisory Board (USEPA, 2006) concluded that PPARα activation may not be the sole MOA for liver tumors caused by PFOA. The recent research discussed above that has become available subsequent to the USEPA Science Advisory Board report (USEPA, 2006) confirms the importance of non-PPARα MOA(s) in the hepatic effects of PFOA. The majority of the SAB panel also believed that the human relevance of the PPARα mode of action for liver tumors caused by PFOA could not be dismissed, based on data indicating similar responses to PFOA in the livers of rodents and primates, including increased liver weight and induction of hepatic peroxisomal enzyme activity (USEPA, 2006).

A "tumor triad" consisting of tumors of the liver, testicular Leydig cells, and pancreatic acinar cells occurred in rats treated with several PPARα activators including PFOA (Biegel et al., 2001, Klaunig et al., 2003). The modes of action of the latter two tumor types are not fully characterized, and the USEPA Science Advisory Board (USEPA, 2006) concluded that they should be presumed relevant to humans.

Some of the developmental and immune effects of PFOA in mice are known to have PPARα dependent or independent MOA(s) (Dewitt et al., 2009; Abbott et al., 2007), while the MOA(s) for neurobehavioral toxicity, delayed mammary gland development, and effects on the female reproductive tract are not known. PPARα, as well as PPAR β and PPAR γ, are expressed in many fetal and adult tissues in rodents and humans, and their patterns of

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expression vary with developmental age (Abbott et al., 2010, in press). Based on their physiological roles, they are expected to have important roles in reproduction and development in these species (Abbott, 2009). However, unlike PFOA, which is considered a low affinity PPARα activator, two higher affinity PPARα activators, WY and clofibrate, had no effect on reproductive and developmental parameters in mice (Palkar et al., 2010).

In the lungs and the liver of fetal (GD 18) CD-1 mice exposed during gestation, PFOA primarily affected the expression of genes related to intermediary metabolism and inflammation, including genes both associated and not associated with PPARα activation (Rosen et al., 2007). The authors suggested that PFOA tends to shift metabolism in the direction of a fasted animal, consistent with the metabolic changes and obesity observed in adulthood in gestationally-exposed mice (Hines et al., 2009). Recently, gestational exposure to PFOA was found to alter the expression pattern of PPARα, β, and γ in many tissues in fetal and neonatal CD-1 mice (Abbott et al., in press). The expression of genes regulated by PPARs, CAR, and PXR, including genes involved with homeostatic control of lipid and glucose metabolism, was also altered by PFOA exposure as early as GD14. The authors suggested that these effects on metabolism could contribute to the neonatal mortality and decreased rate of growth caused by gestational exposure to PFOA.

Peripubertal exposure to PFOA stimulated mammary gland development equally in C57Bl/6 wild type and PPARα null mice, indicating that this effect is independent of PPARα (Zhao et al., 2010). However, the role of PPARα in the delayed mammary gland development caused by developmental exposures in CD-1 mice is not known. PPARα null (KO) mice are viable, healthy, and fertile (Lee et al., 1995), suggesting that PPARα is not required for mammary gland development (Yang et al., 2006). In contrast, mammary gland development was impaired in mice with constitutively activated PPARα and in pregnant WT mice administered the PPARα activator WY, but not in pregnant PPARα null (KO) mice similarly treated with WY (Yang et al., 2006).

Estrogenic activity and/or increases in estrogen levels may be involved in the MOA for PFOA. Estradiol was increased in male Sprague-Dawley rats chronically exposed to PFOA (Biegel et al., 2001), and PFOA shows estrogenic activity in the fish species, rare minnow (Wei et al., 2007; 2008). Studies in rainbow trout, which have long been used as a model for human liver carcinogenesis because they are insensitive to peroxisome proliferation, suggest that PFOA promotes liver tumor development through an estrogenic mechanism (Tilton et al., 2008; Hemmer et al., 2010; Benninghoff et al., 2011).

Finally, a recent study (Suh et al., 2011) suggests that reduced placental efficiency due to effects on placental trophoblast cells and placental hormones may play a role in PFOA's developmental effects such as fetal growth retardation in mice.

9. Other perfluorinated chemicals

Although the scope of this review is limited to PFOA, it must be emphasized that PFOA is just one member of the larger group of perfluorinated chemicals (PFCs) with different chain lengths and functional groups. Many of the reviews cited in the introduction (Section 1) and other papers cited throughout include information on PFOS and/or other PFCs, as well as PFOA. The terminology, production, and interrelationships between compounds for a large number of PFCs and related compounds were recently reviewed by Buck et al. (2011).

PFOS and other PFCs are found in drinking water and other environmental media (ATSDR, 2009; Ericson et al., 2008; Konwick et al., 2008; Mak et al., 2009; Murakami et al., 2008; Nakayama et al., 2007; Nakayama et al., 2010; Wilhelm et al., 2010), as well as human serum (Calafat et al., 2007; Toms et al., 2009; Zhang et al., 2010) in the U.S. and worldwide. As part of the voluntary stewardship effort by major manufacturers to reduce the use of PFOA (USEPA, 2009a), new perfluorinated and polyfluorinated compounds, including shorter chain length PFCs, are being developed as alternatives to PFOA, PFOS, and other long chain perfluorinated compounds (USEPA, 2010c).

PFOS has been extensively studied, and much information is available on its environmental occurrence and fate, human exposure, animal toxicity, and associations with health endpoints in human populations. Global production of PFOS by its major U.S. manufacturer was phased out in 2002, although production by other companies overseas has increased since that time (USEPA, 2009a). In contrast to PFOA, U.S. serum levels in NHANES have declined markedly, coinciding with this phase out, from a geometric mean of 30.4 ng/mL in 1999–2000 to 13.2 ng/mL in 2001–2008 (Kato et al., 2011).

The extensive data on PFOA and PFOS, along with the more limited information currently available on other PFCs, suggest that the toxicological potencies and human half-lives of PFCs vary widely and that there are both similarities and differences in toxicological effects and modes of action among these compounds (Lau et al., 2007: ATSDR, 2009; Peters and Gonzalez, 2011; Wolf et al., in press; Naile et al., 2012). Approaches for assessing the risks of PFCs as a group may be developed in the future so that the potential health effects of environmental mixtures of these compounds can be addressed (USEPA, 2009a). Any such approach should consider the qualitative and quantitative differences in the toxicities of the individual PFCs.

10. Discussion

The information presented in this review indicates that PFOA differs in several important ways from other well-studied drinking water contaminants. PFOA is very resistant to degradation in the environment and thus persists indefinitely (Section 1). Unlike other persistent, bioaccumulative, and toxic organic compounds that are fat soluble and for which human exposure primarily occurs through dietary sources such as fish, meat, or dairy products, PFOA is water soluble and contaminates drinking water sources when discharged to the environment (Sections 1 and 4.2).

PFOA has been frequently found in drinking water, but current information is insufficient to make meaningful conclusions about PFOA's overall occurrence and general population exposure from drinking water in the U.S. and most other countries (Section 3). Many of the studies of drinking water and source water were not general surveys, but rather focused on specific regions or on sites known or suspected to be contaminated. In the U.S., PFOA and five other PFCs are listed in the proposed Unregulated Contaminant Monitoring Rule 3 (USEPA, 2011) which, if finalized as proposed, will ultimately provide information on nationwide occurrence in public water supplies.

PFOA has a half-life of several years in humans (Section 5), and ongoing exposure to relatively low levels in drinking water substantially increases total exposure in humans (Sections 4.2.1 and 5.1). Exposure in infants (breast-fed or formula-fed), a potentially sensitive subpopulation, is higher than in adults using the same drinking water source due to PFOA's presence in breast milk and the greater drinking water intake of infants on a body weight basis (Section 5.2). Because of its long human half-life, an elevated body burden resulting from exposure to contaminated drinking water will not return to background levels for several years after exposure ceases (Section 5).

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Much of the data from humans and animals are very recent, and additional findings are continually emerging at a rapid pace. Some endpoints associated with PFOA exposure in humans are similar to effects seen in experimental animals, while for other effects such as lipid metabolism, humans and laboratory animals appear to react differently to PFOA (Section 6). Unlike most other well-studied drinking water contaminants, the dose response curve for several effects in epidemiology studies appears steepest at the lower exposure levels, including the range of serum levels found in the general population, with no threshold identified (Section 6.1). The consistency between results of studies in different populations, the clinical importance of many of the endpoints for which associations are observed, and the observation of associations within the exposure range of the general population suggest the potential for health effects from exposures through drinking water. Because of the design of the epidemiology studies reported to date, the results cannot be clearly interpreted as demonstrating a causal relationship, but the consistency of findings strongly suggests a causal relationship for at least some endpoints.

PFOA has been classified as likely to be carcinogenic to humans by the USEPA Science Advisory Board (USEPA, 2006) although there is some uncertainty about the human relevance of some of the animal tumor data. Results of cancer incidence studies in communities with contaminated drinking water are forthcoming.

Recent animal data reveal a variety of other toxicological effects, including some that occur after exposure to low doses during development, with no threshold (NOAEL) identified. These include persistent changes in the mammary gland, histopathological changes in the female reproductive tract, persistent neurobehavioral effects, and obesity and metabolic changes in adulthood (Section 6.2). Some of these effects are not evident until later in life and/or adulthood, long after the administered PFOA has been eliminated from the body. Several of these endpoints did not occur when the doses that caused toxicity from developmental exposure were administered to adult mice, while the effects of exposure during adulthood have not been evaluated for other endpoints. Based on current knowledge of PFOA's mode of action, the potential for human relevance of these effects cannot be discounted (Section 8).

For most other drinking water contaminants, doses that cause effects in animal studies are much higher than human environmental exposures. However, impaired mammary gland development in mice (White et al., 2011b) resulted from developmental exposure to a concentration of PFOA in drinking water relevant to that found in exposed communities and at a serum level within twofold of the upper range of the general population (NHANES data, Kato et al., 2011). Such effects that occur later in life as a result of prenatal or early-life exposures are more difficult and time-consuming to detect in epidemiology studies than effects that occur concurrently with exposure. Notably, prenatal PFOA exposure was recently reported to be associated with increased risk of overweight/obesity and changes in metabolic hormones in 20-year old women (Halldorsson et al., 2012), consistent with data from adult female mice exposed only during development (Hines et al., 2009). Results of ongoing prospective studies (C8 Science Panel, 2011d) and analyses of associations of effects with estimated past exposures (Shin et al., 2011) are expected to provide additional information relevant to this issue.

Although numerous recent studies have provided important new information on PFOA's effects in animals and humans, environmental occurrence, and sources of human exposure, many uncertainties and data gaps remain to be addressed by future research. For example, studies in additional communities with environmental exposures would be valuable to determine whether the associations seen in the C8 Health Study population are confirmed. Additionally, results of chronic toxicology studies have been published only from the rat, a species in which PFOA is rapidly excreted by females. Chronic studies in another species in which PFOA is persistent in both sexes, such as the mouse, would provide important information specific to females, particularly in regard to chronic effects including carcinogenicity. Furthermore, the currrently available chronic studies did not assess effects including carcinogenicity which might result from exposures during the critical developmental stages now known to be sensitive periods for PFOA toxicity. In its recent review of the current evidence on environmental risk factors for breast cancer, the Institute of Medicine of the National Academy of Sciences (IOM, 2011) concluded that currently available data suggest the possibility of a link between PFOA exposure and breast cancer. They state that that "the potential carcinogenicity of PFOA in the mammary gland [e.g. (Sibinski, 1987)] and effects of exposure [on mammary gland development] during various stages of life provide biologic plausibility to the hypothesis that PFOA may impact breast cancer and remain important topics for future research."

Finally, little is currently known about isomer-specific exposures and effects of PFOA, or how differences in isomer profiles may have influenced the outcomes of previously reported studies in animals and humans.

11. Conclusions

This paper critically reviews recent information relevant to the assessment of PFOA as an emerging drinking water contaminant. PFOA is commonly found in finished drinking water and drinking water sources, but the overall frequency of occurrence and population exposed from drinking water is unknown. PFOA, as well as some other PFCs, are distinguished from most other organic drinking water contaminants by their extreme environmental persistence and long human half-life. Serum levels of PFOA are increased by ongoing drinking water exposure, with an average serum:drinking water ratio of about 100:1. For example, ongoing exposures to drinking water concentrations of 10 ng/L, 40 ng/L, 100 ng/L, or 400 ng/L are expected to increase average serum levels by about 25%, 100%, 250%, and 1000%, respectively, from the general population background of about 4 ng/mL. PFOA causes several types of toxicity in experimental animals, including low dose developmental effects, some of which persist into adulthood. In humans, PFOA is associated with numerous health endpoints within the exposure range of the general population, as well as in more highly exposed groups. As is the case for most such epidemiology studies, causality is not proven for these effects. Infants are potentially a sensitive subpopulation for PFOA's developmental effects; exposure to infants, either directly through water ingestion or indirectly through breast milk, is higher than in adults using the same drinking water source. In summary, the information reviewed in this paper suggests that continued human exposure to even relatively low concentrations of PFOA in drinking water results in elevated body burdens that may increase the risk of health effects.

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